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Baldino et al.

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(54) **AMINOPYRIMIDINE KINASE INHIBITORS**

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(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

This patent is subject to a terminal disclaimer.

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(65) **Prior Publication Data**

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Related U.S. Application Data

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(51) **Int. Cl.**

A61K 31/497	(2006.01)
A61K 31/5377	(2006.01)
A61K 31/535	(2006.01)
A61K 31/55	(2006.01)
A61K 31/517	(2006.01)
A61K 31/495	(2006.01)
A61K 31/52	(2006.01)
C07D 417/14	(2006.01)
C12N 9/99	(2006.01)
C07D 417/06	(2006.01)
C07D 471/04	(2006.01)
C07D 487/04	(2006.01)

(52) **U.S. Cl.**

CPC ***C12N 9/99*** (2013.01); ***C07D 417/06*** (2013.01); ***C07D 417/14*** (2013.01); ***C07D 471/04*** (2013.01); ***C07D 487/04*** (2013.01)

(58) **Field of Classification Search**

CPC C07D 417/14; A61K 31/497; A61K 31/5377; A61K 31/535; A61K 31/55; A61K 31/517; A61K 31/495; A61K 31/52

USPC 514/210.2, 252.18, 252.19, 275, 235.8, 514/218, 266.2, 214.02, 248, 263.21

See application file for complete search history.

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Assistant Examiner — Ebenezer O Sackey
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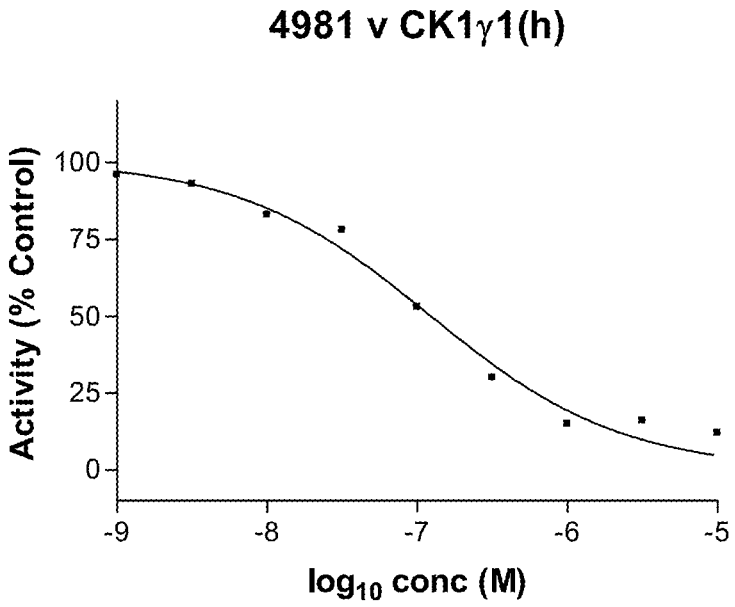
(57) **ABSTRACT**

Disclosed are compounds, pharmaceutical compositions containing those compounds, and uses of the compounds and compositions as modulators of casein kinase 1 (e.g., CK1γ), casein kinase 2 (CK2), Pim1, Pim2, Pim3, the TGFβ pathway, the Wnt pathway, the JAK/STAT pathway, and/or the mTOR pathway. Uses are also disclosed for the treatment or prevention of a range of therapeutic indications due at least in part to aberrant physiological activity of casein kinase 1 (e.g., CK1γ), casein kinase 2 (CK2), Pim1, Pim2, Pim3, the TGFβ pathway, the Wnt pathway, the JAK/STAT pathway, and/or the mTOR pathway.

14 Claims, 27 Drawing Sheets

Figure 1



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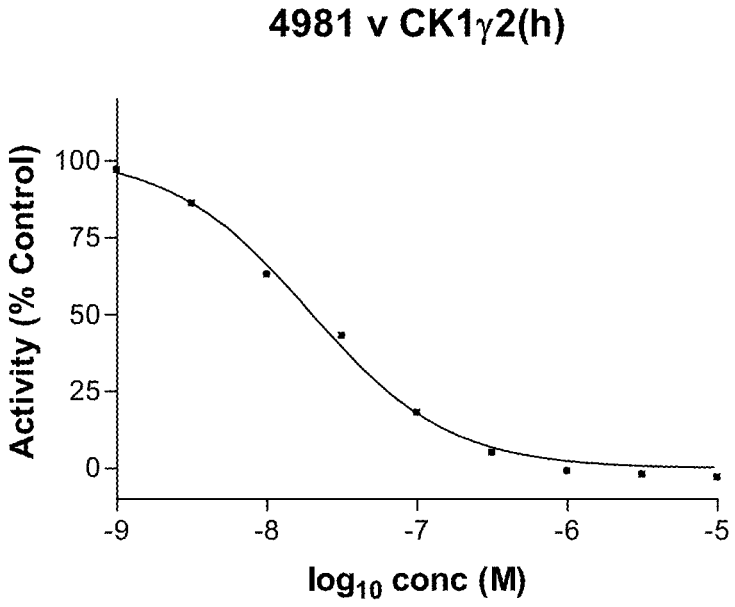

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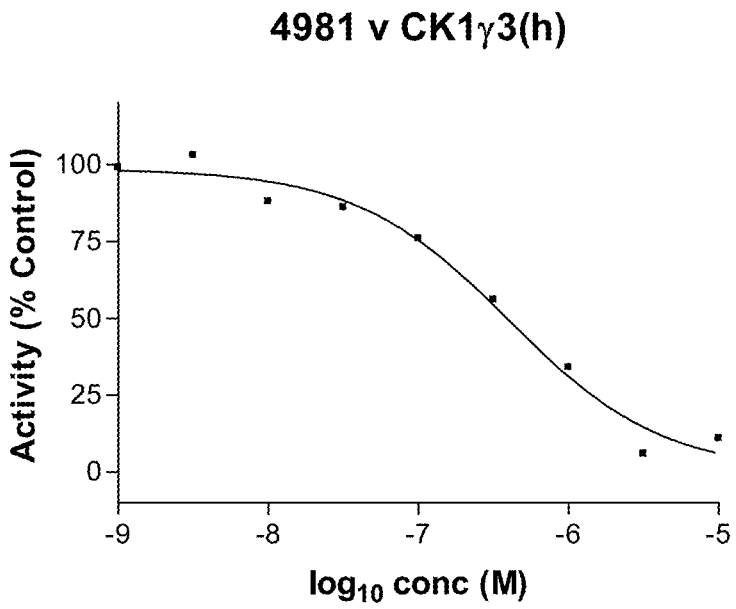

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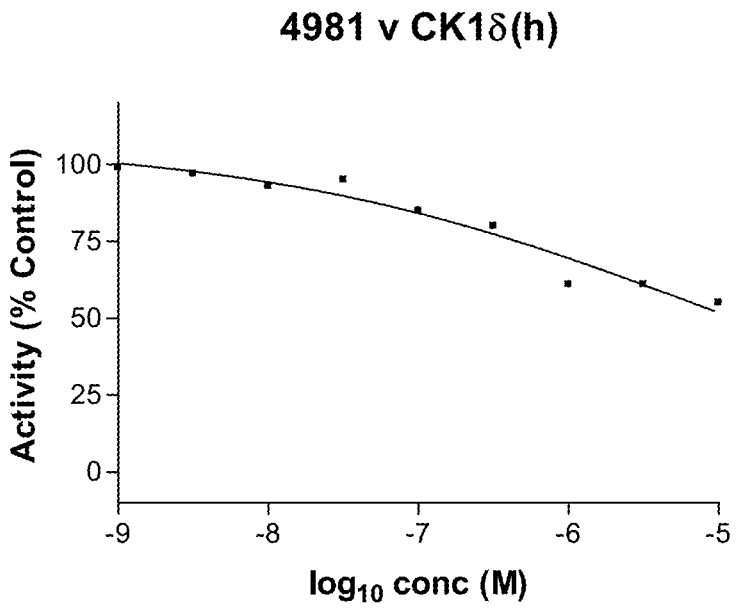

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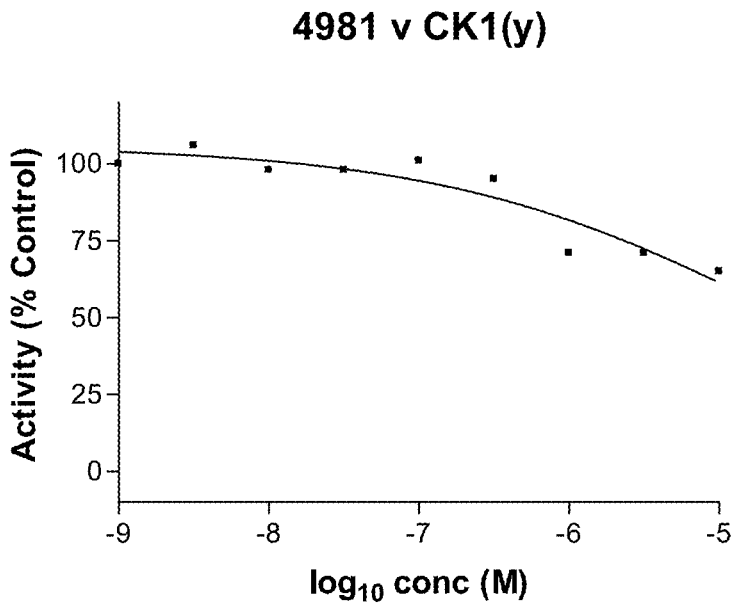

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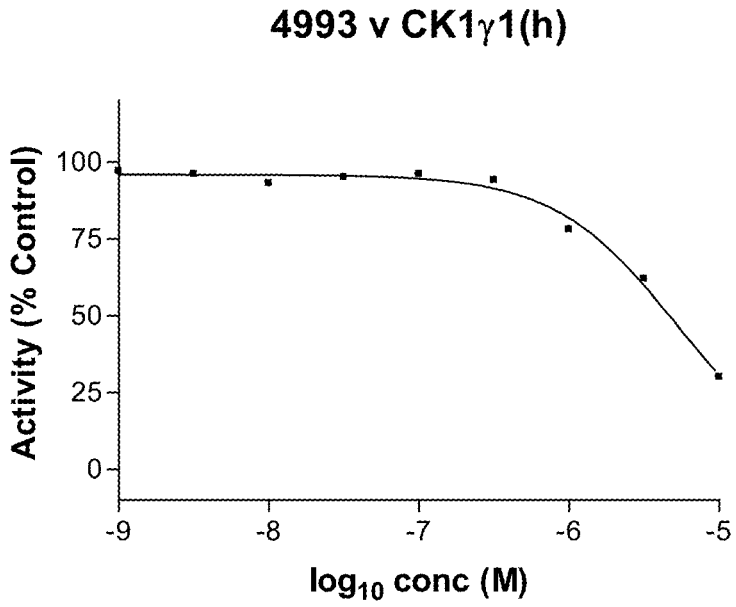

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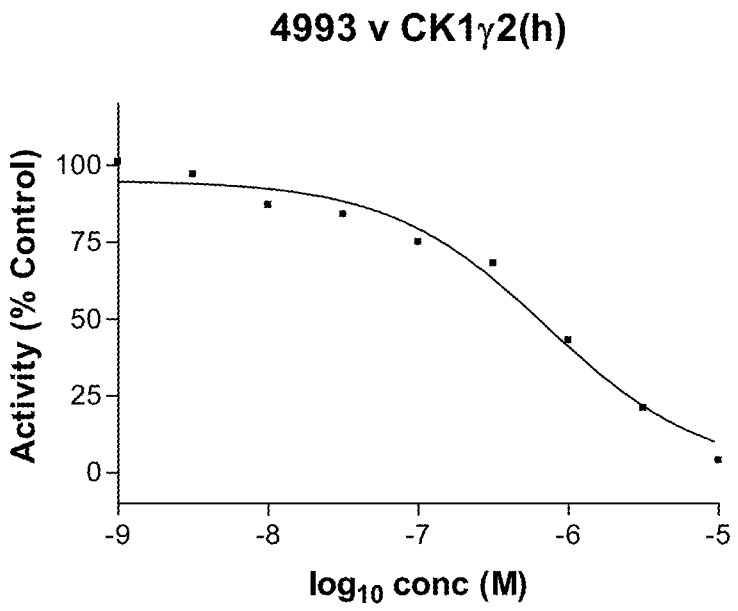

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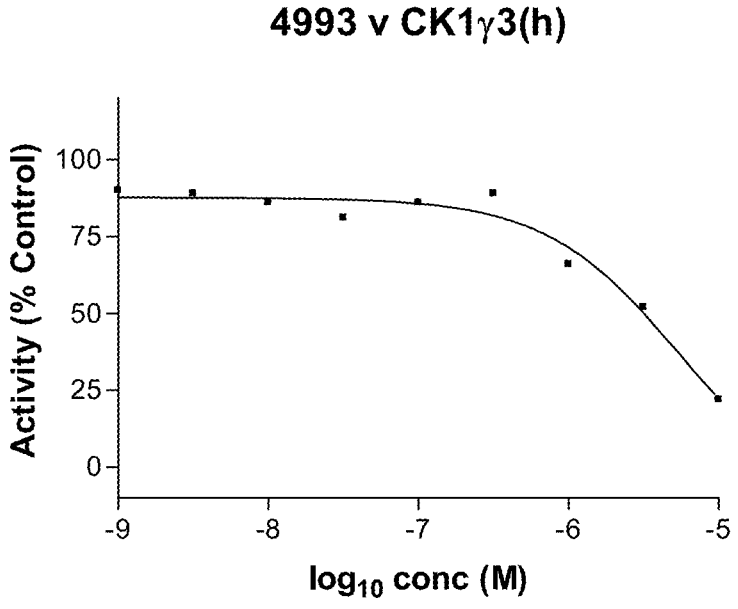

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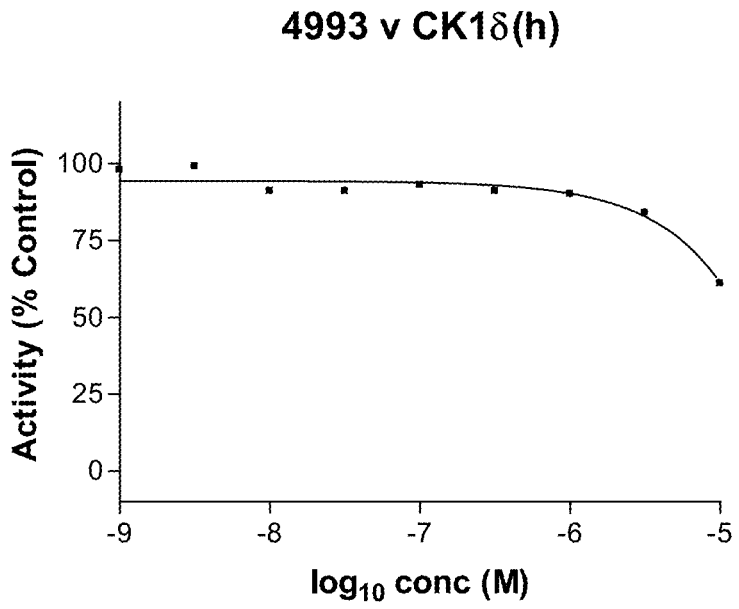

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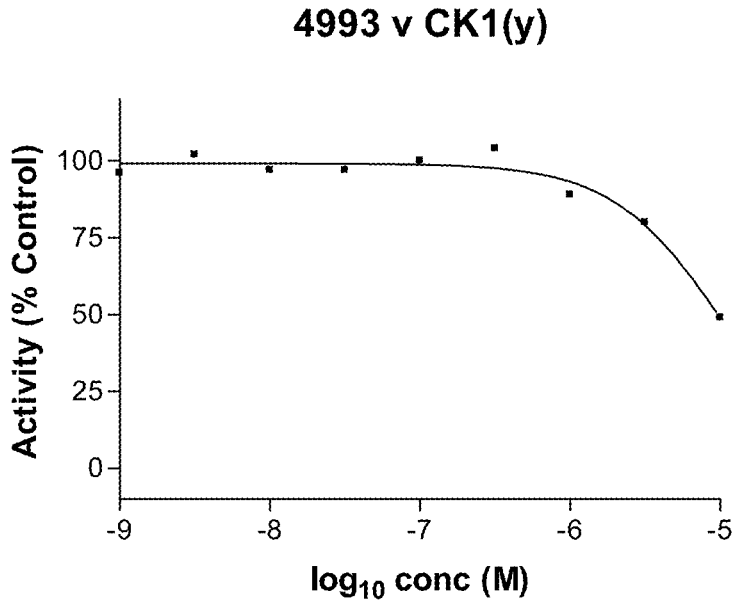

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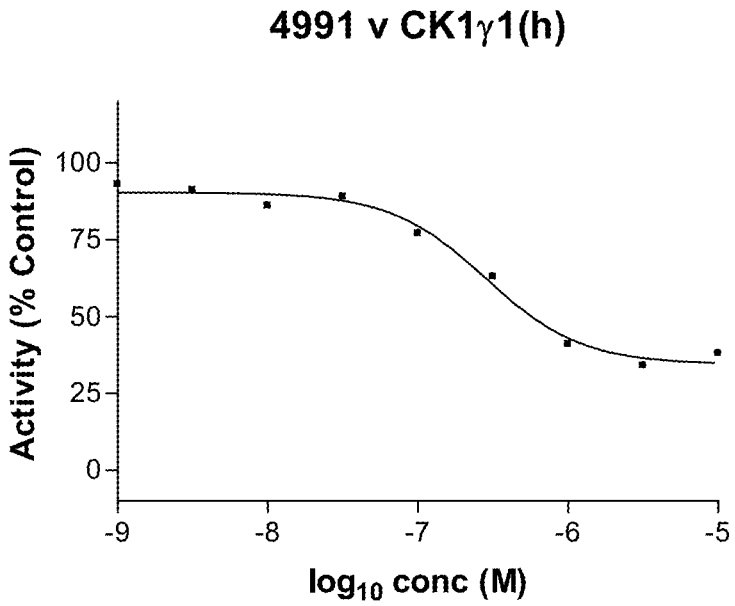

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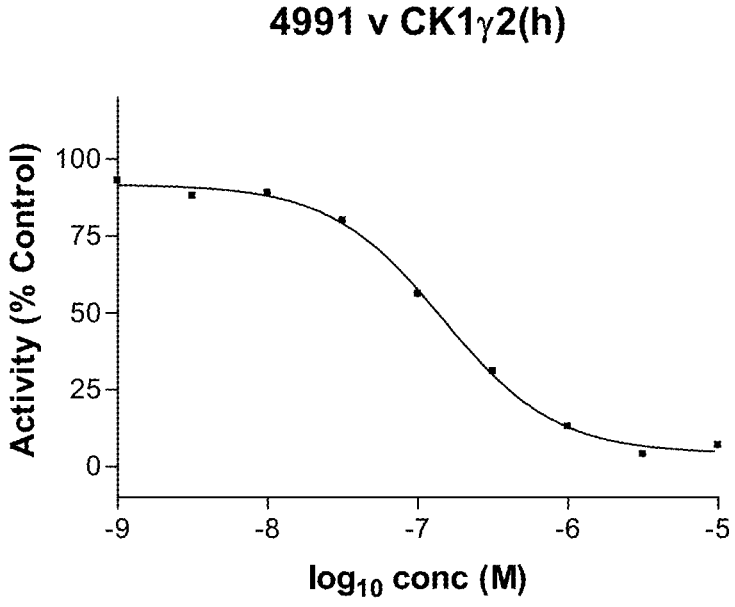

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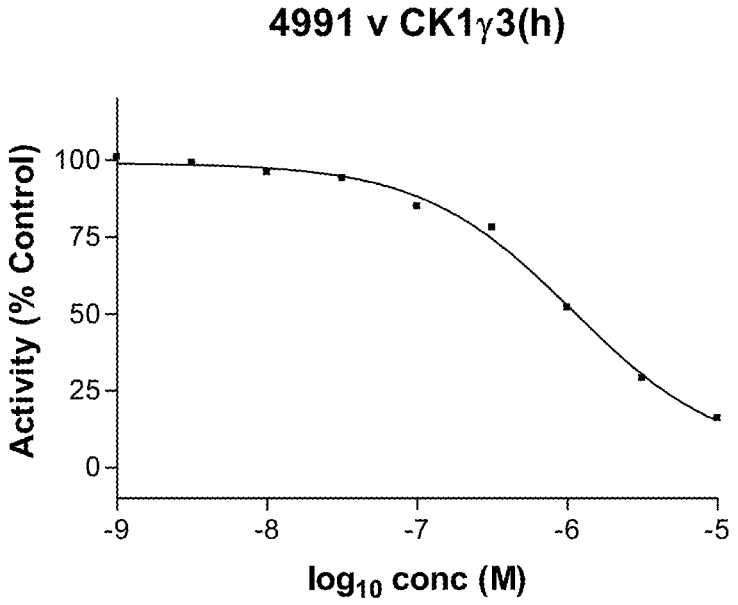

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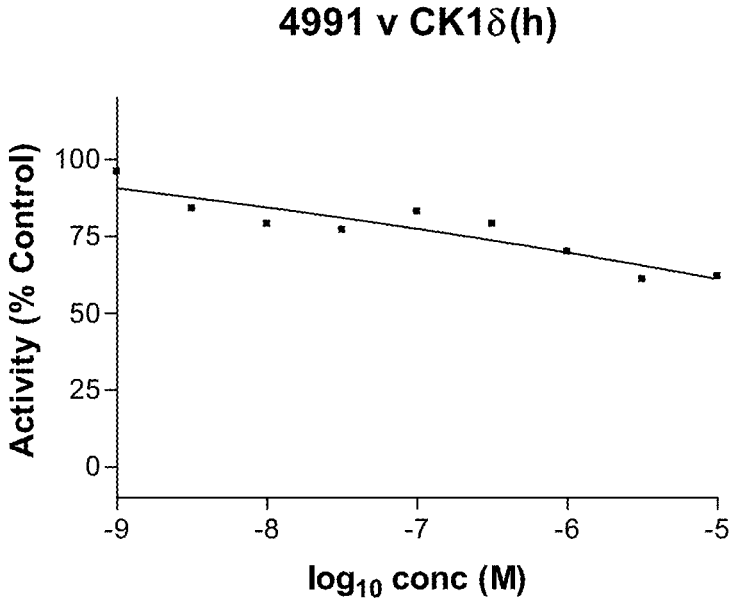

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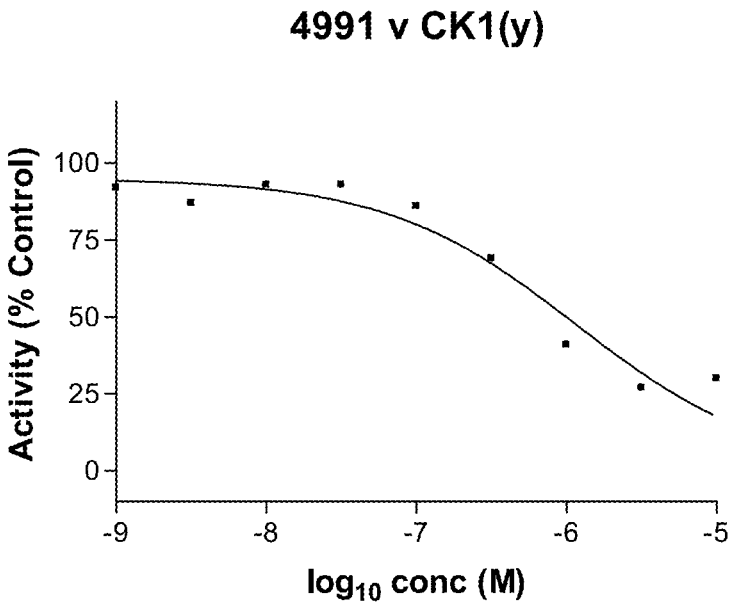

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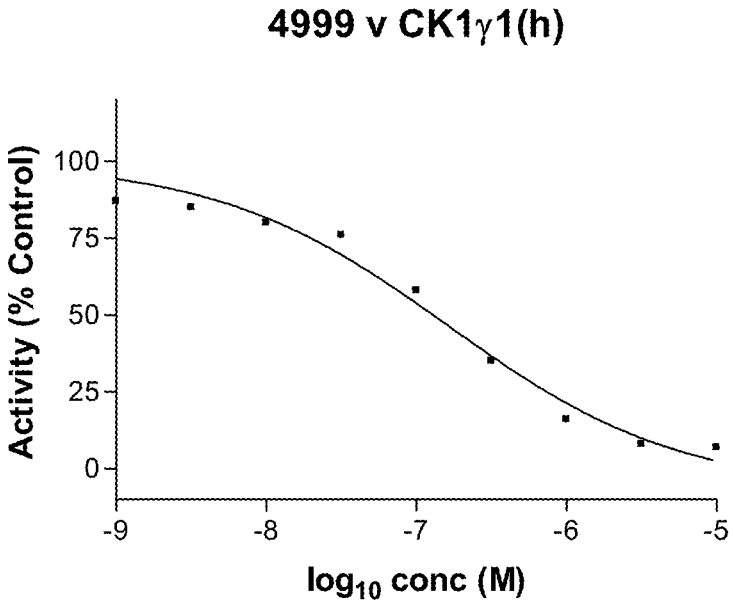

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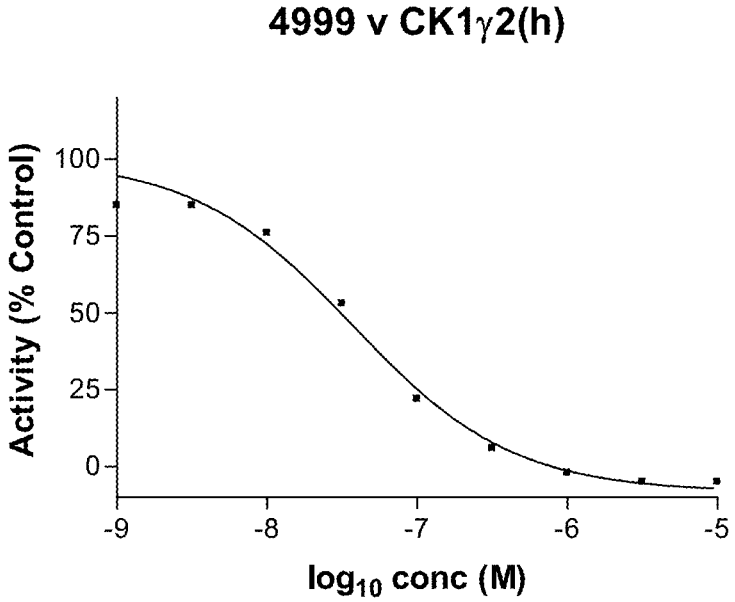

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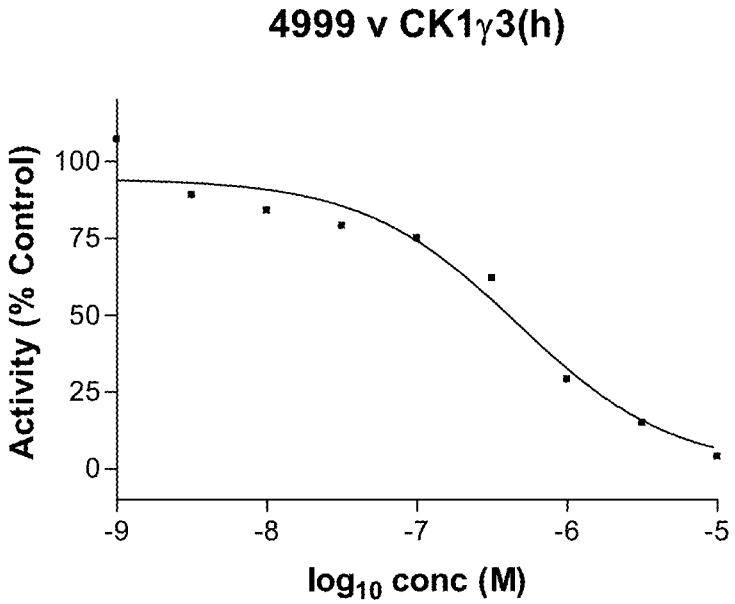

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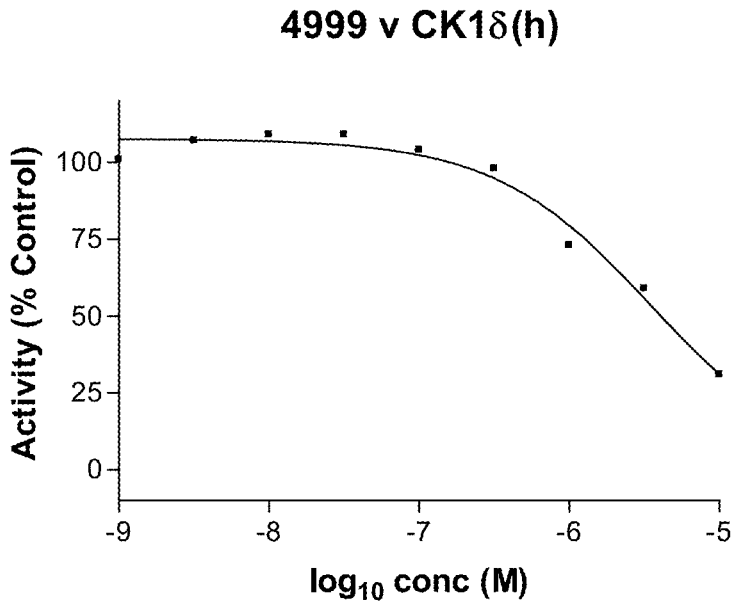

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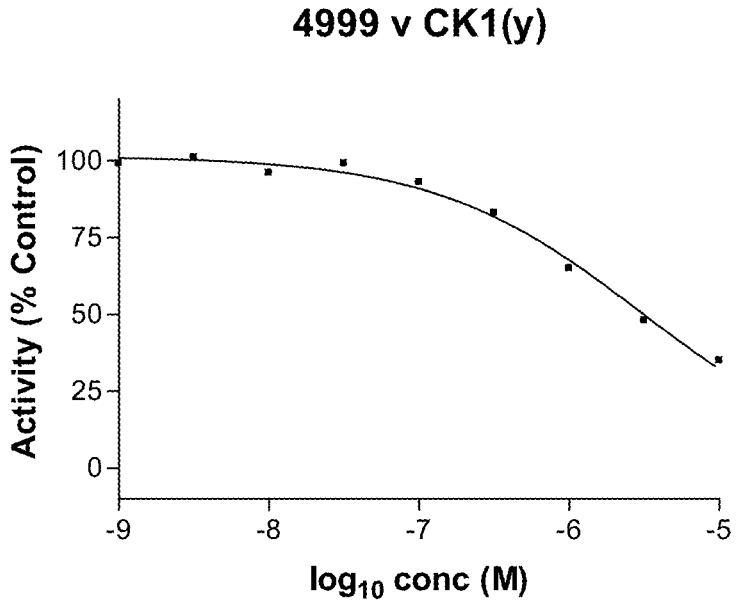

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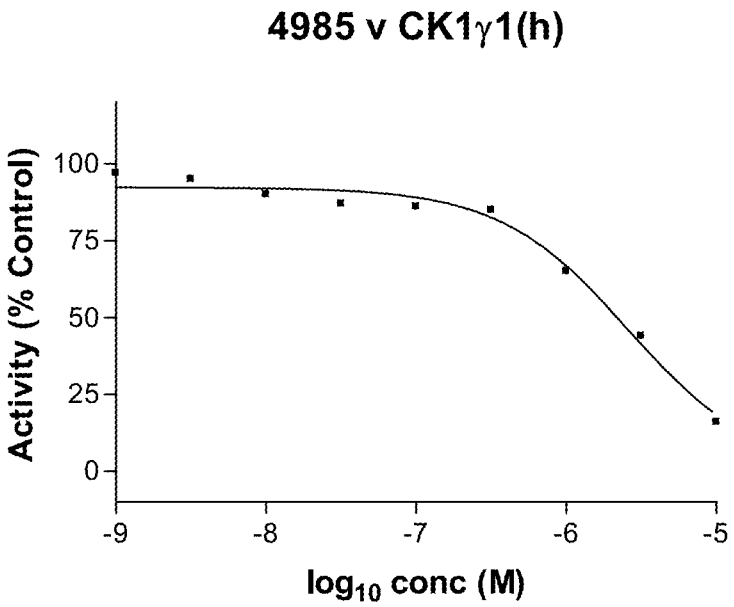

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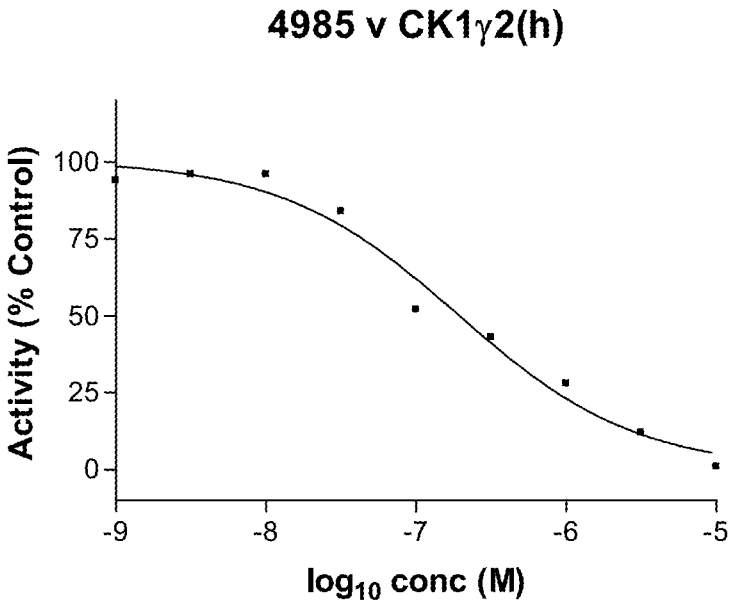

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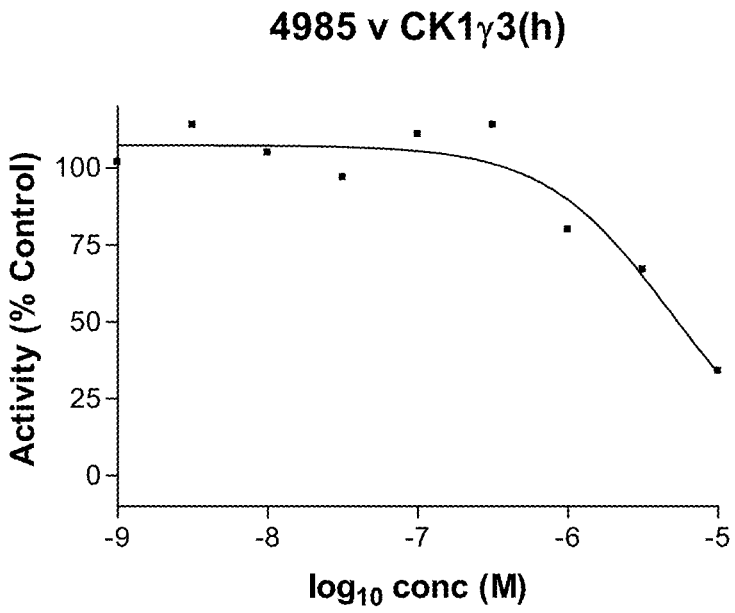

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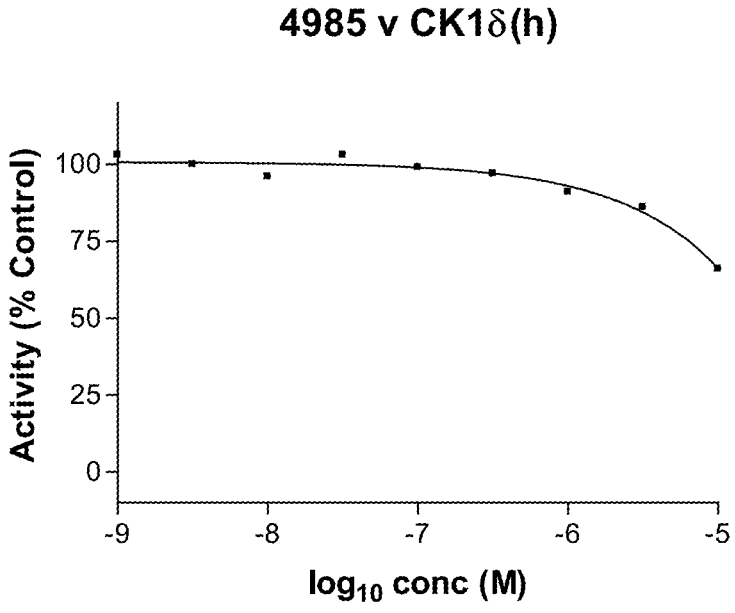

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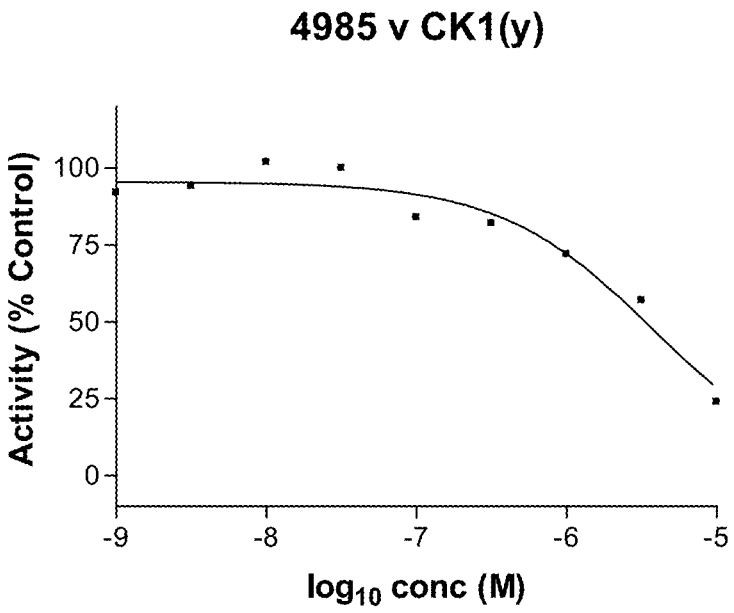

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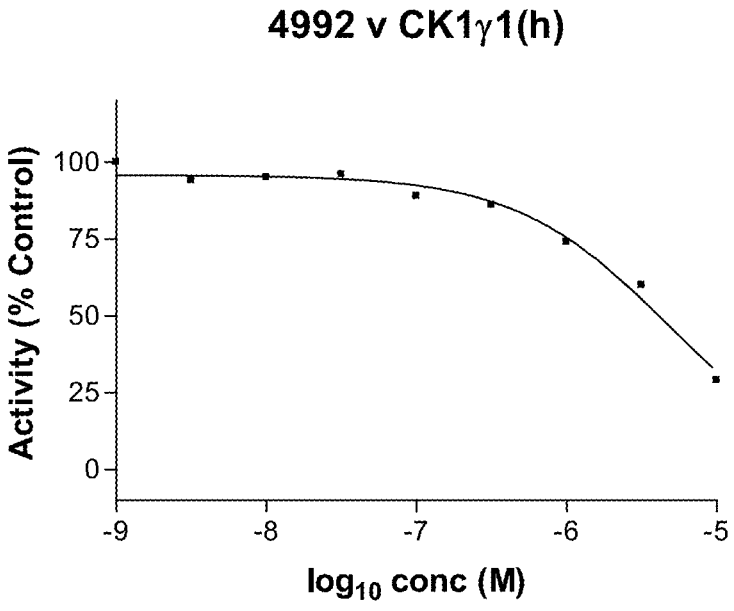

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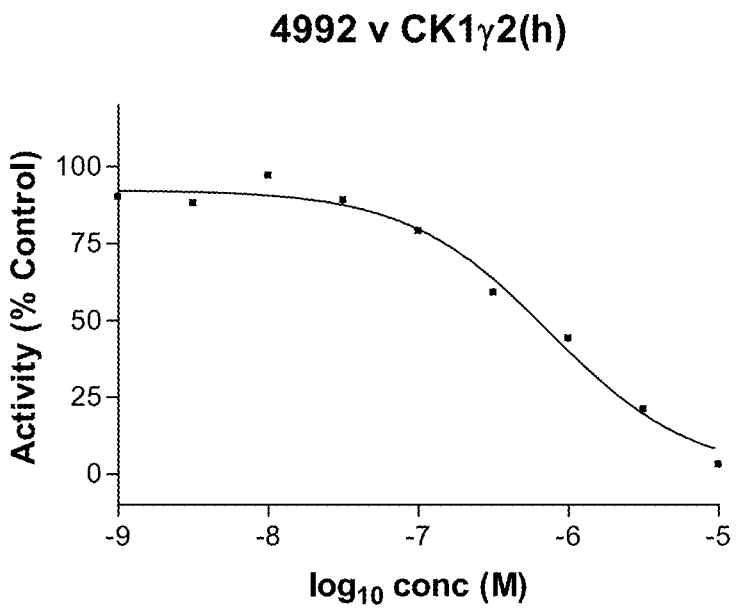

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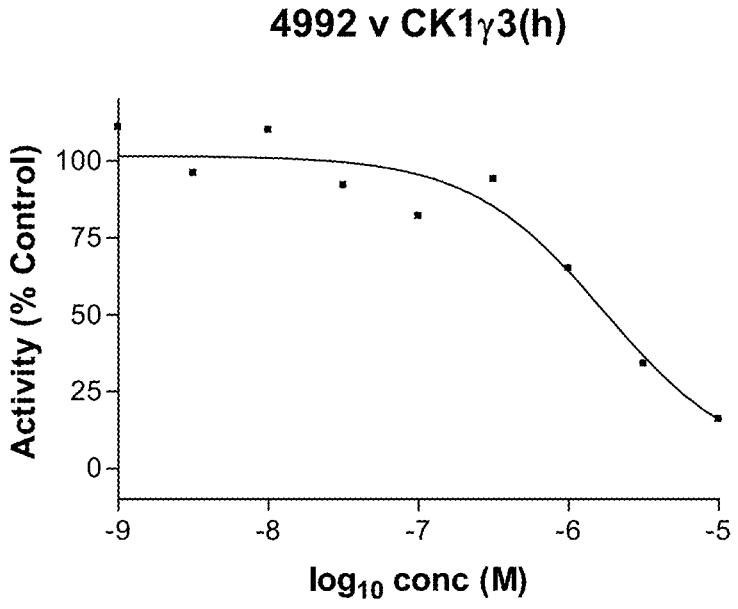

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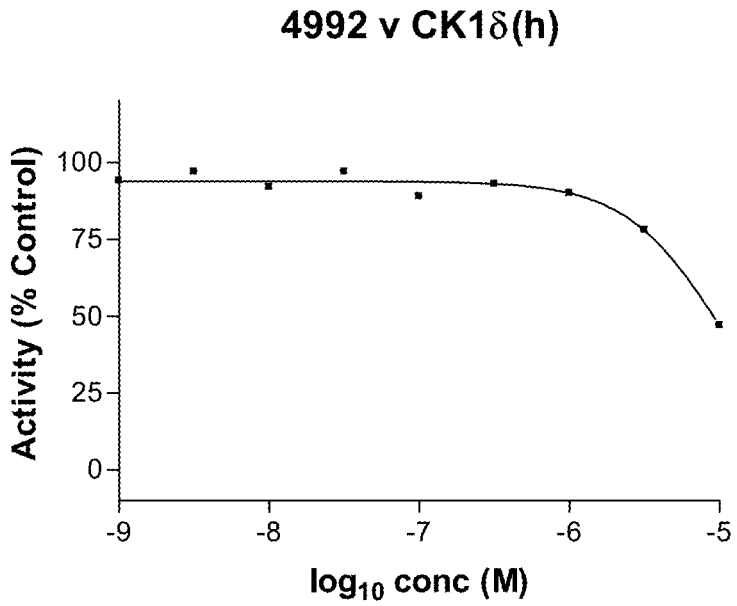

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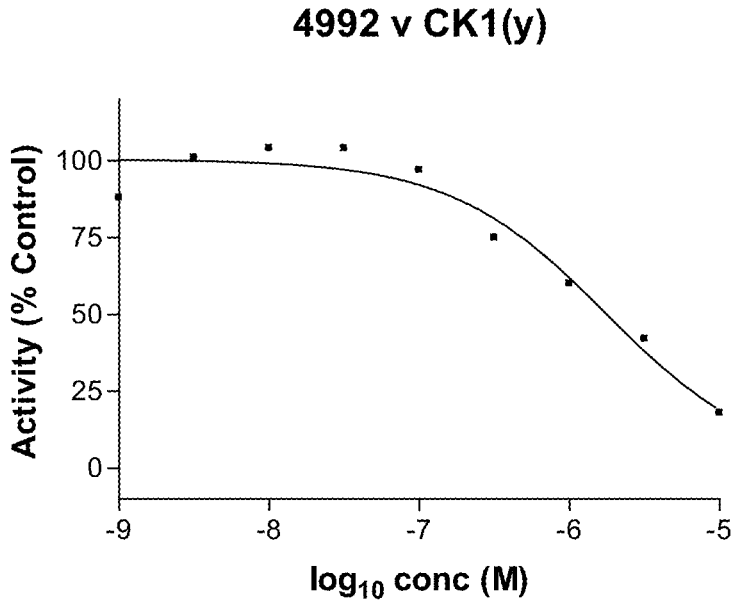

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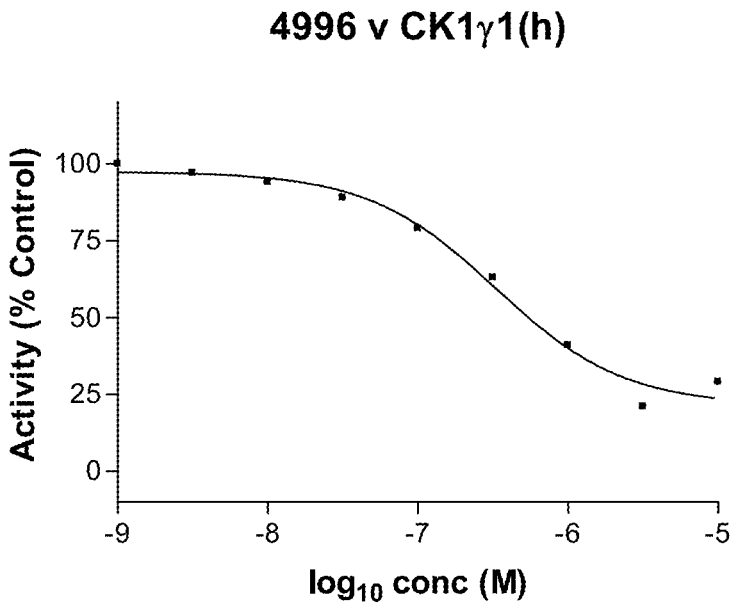

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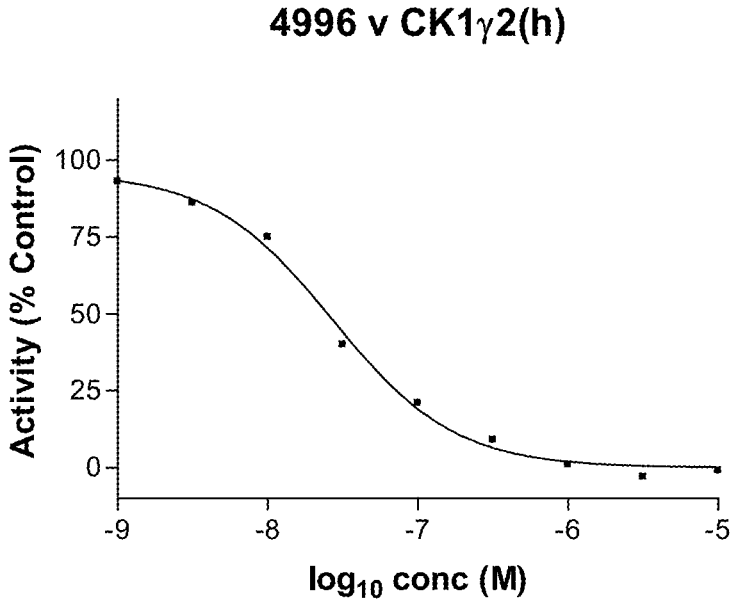

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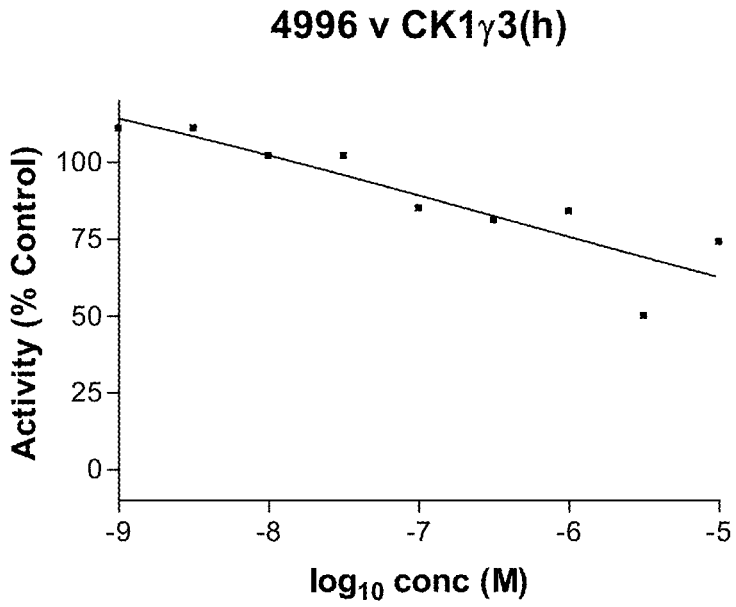

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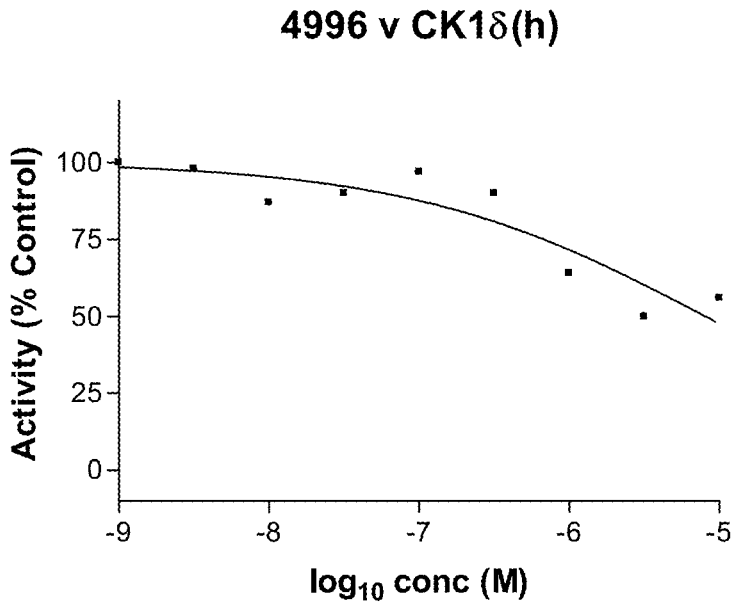

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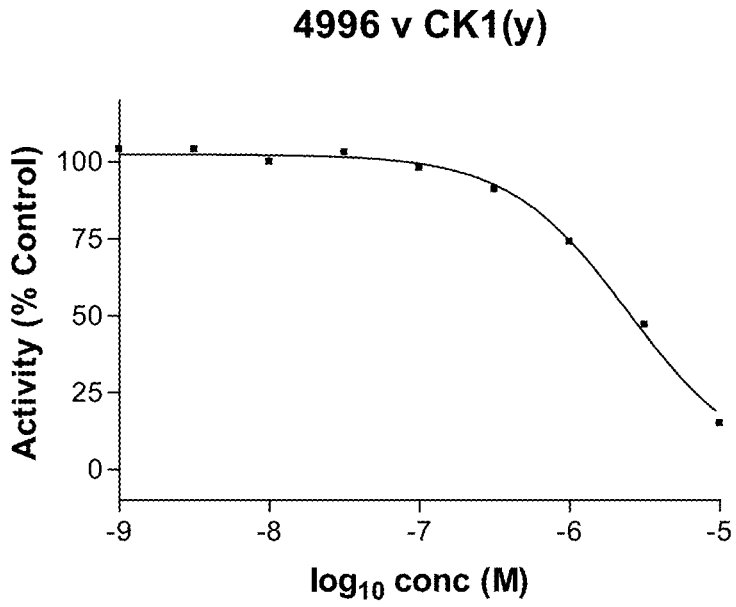

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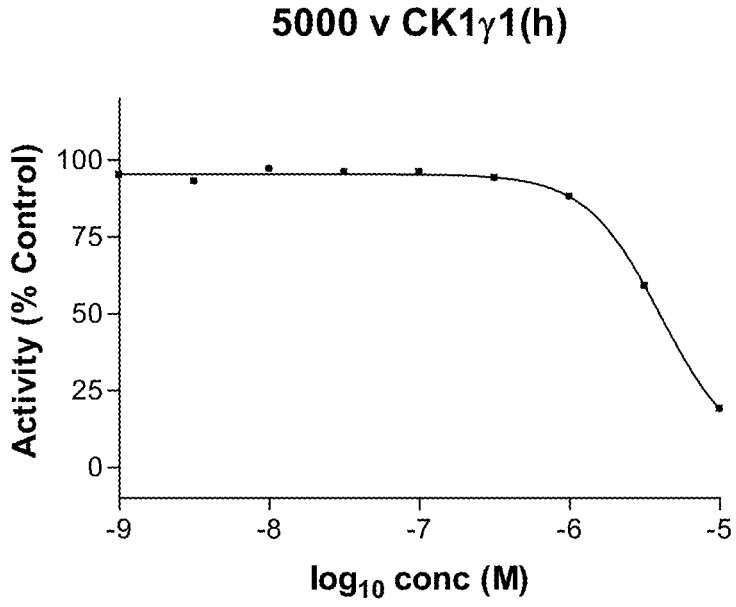

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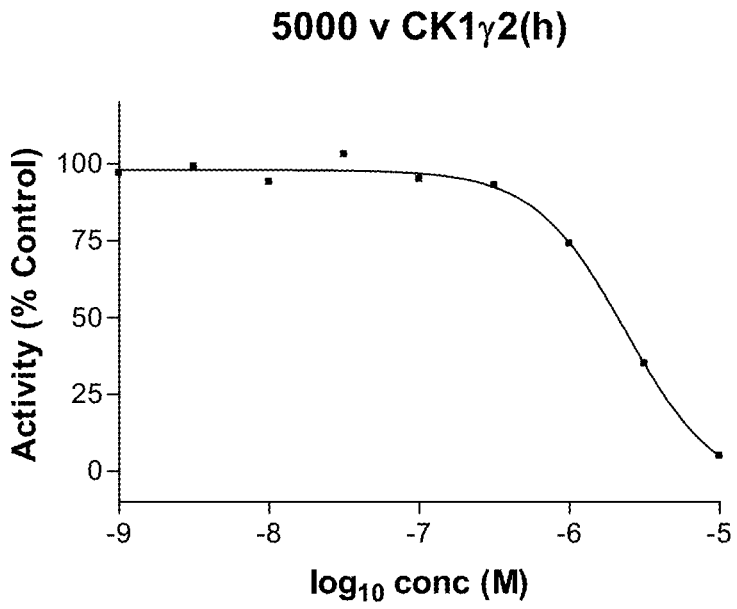

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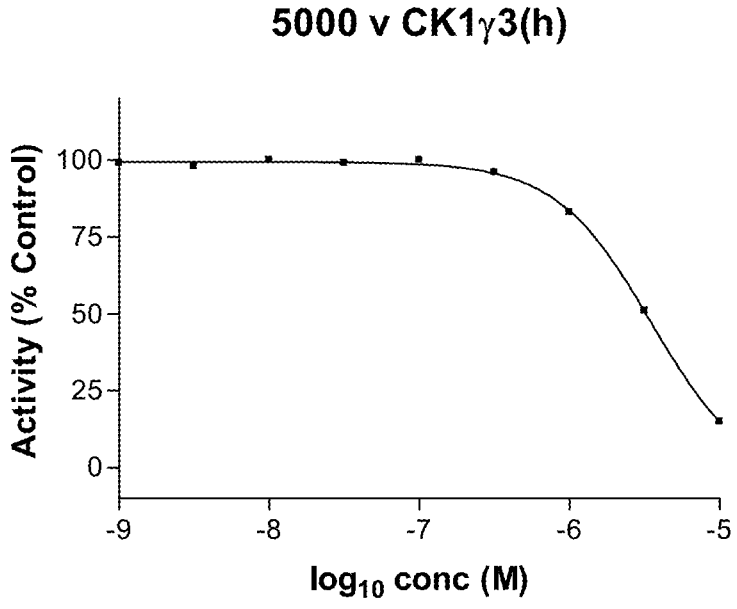

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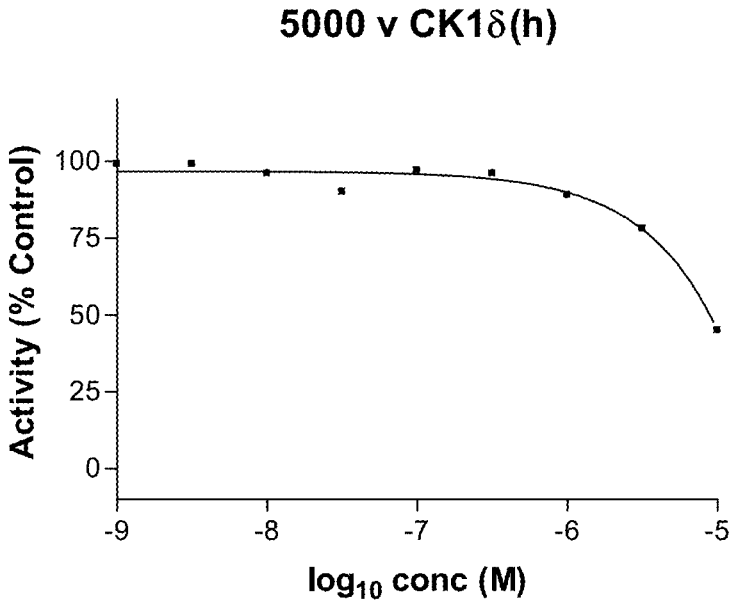

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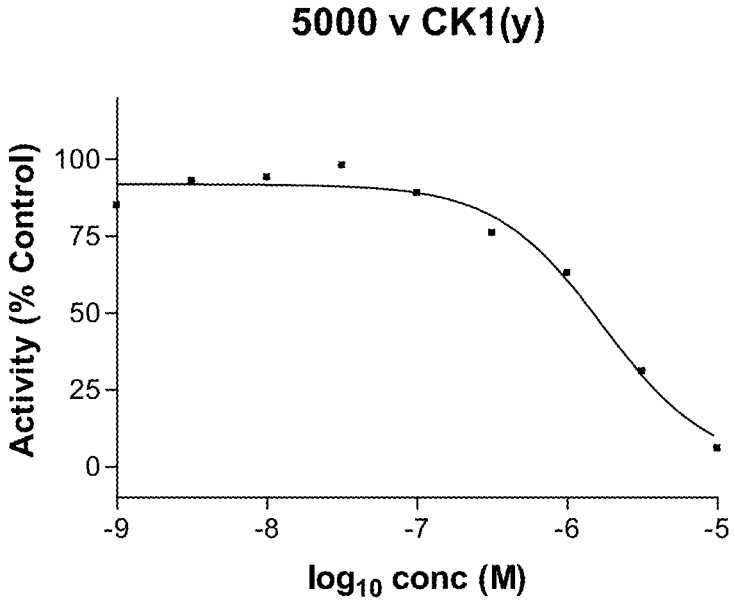

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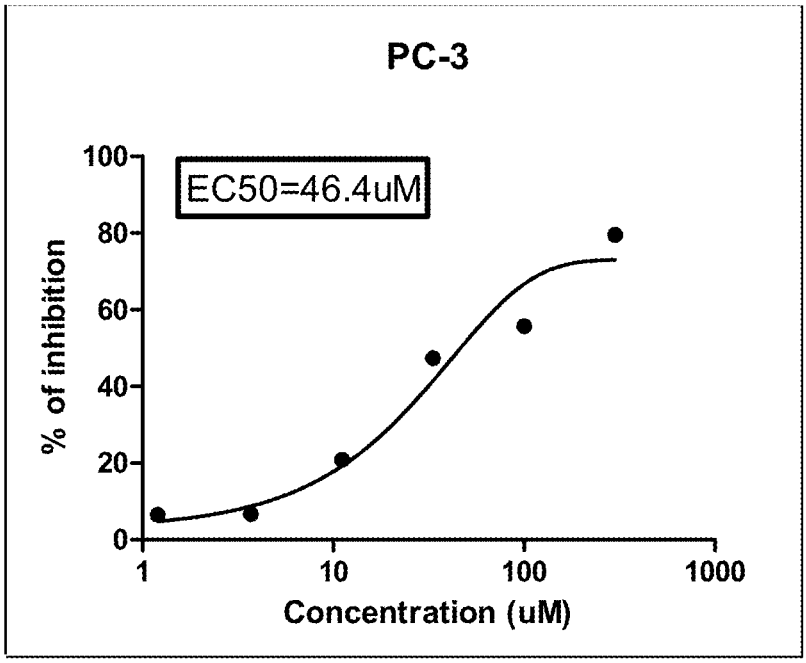

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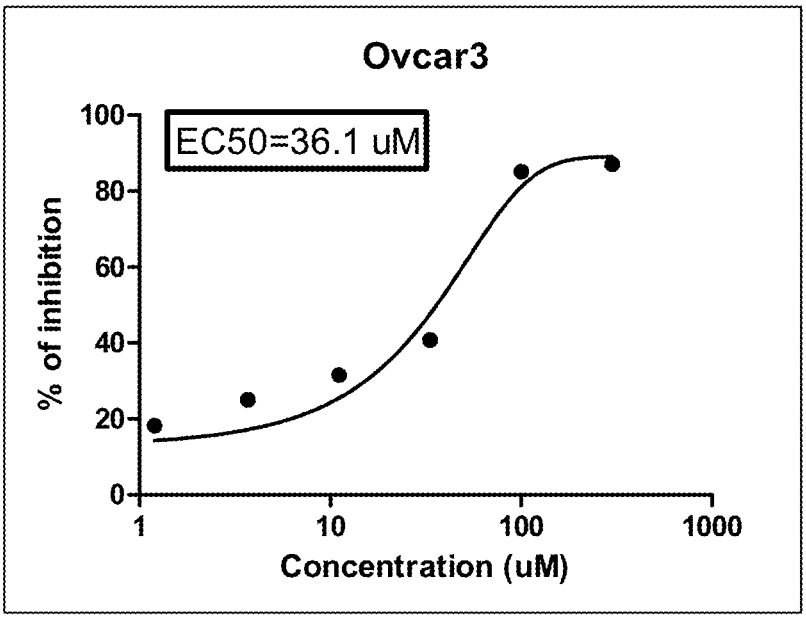

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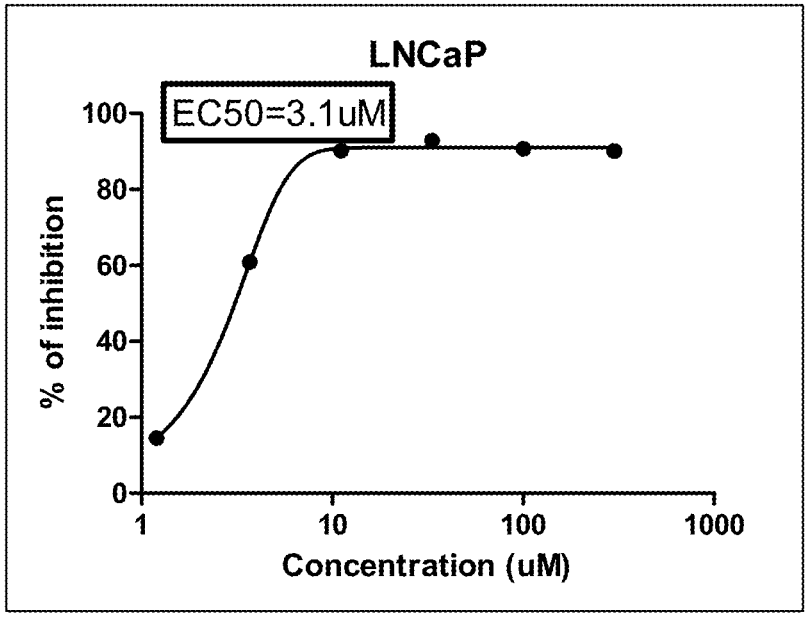

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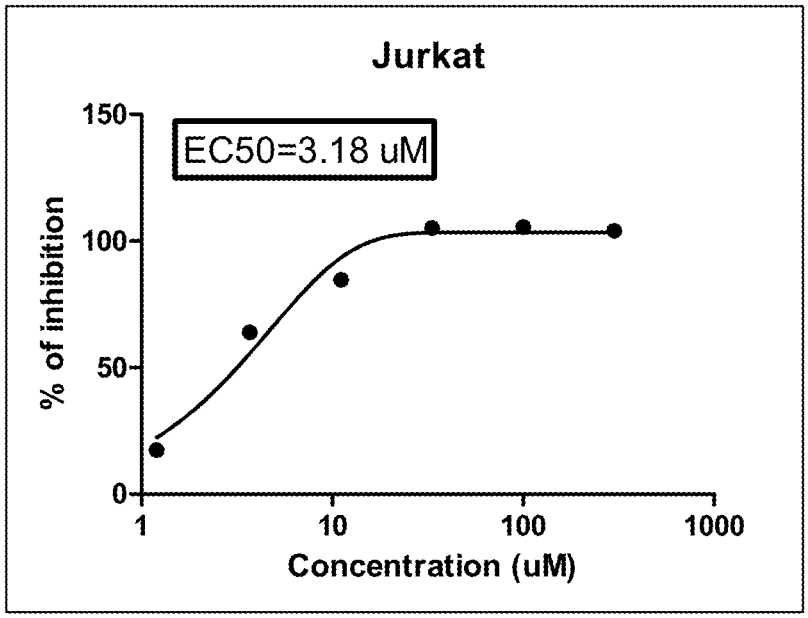

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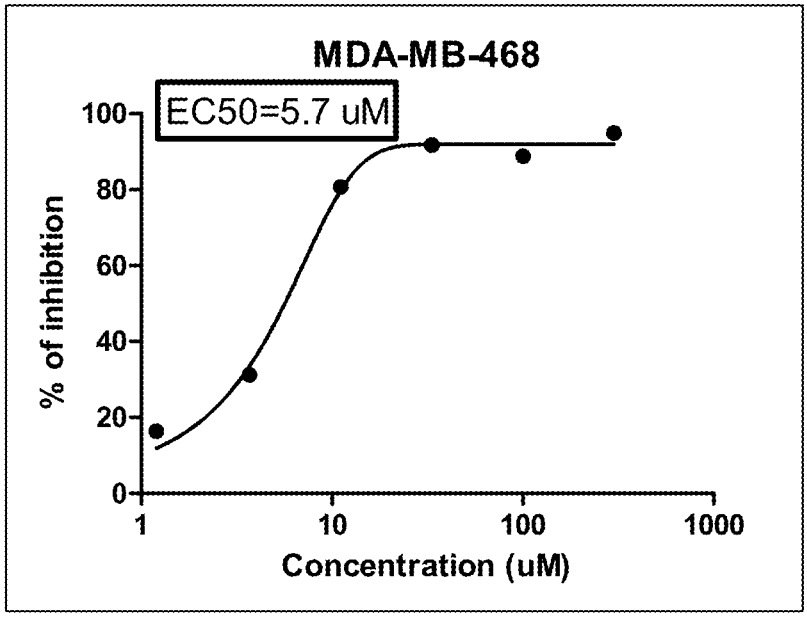

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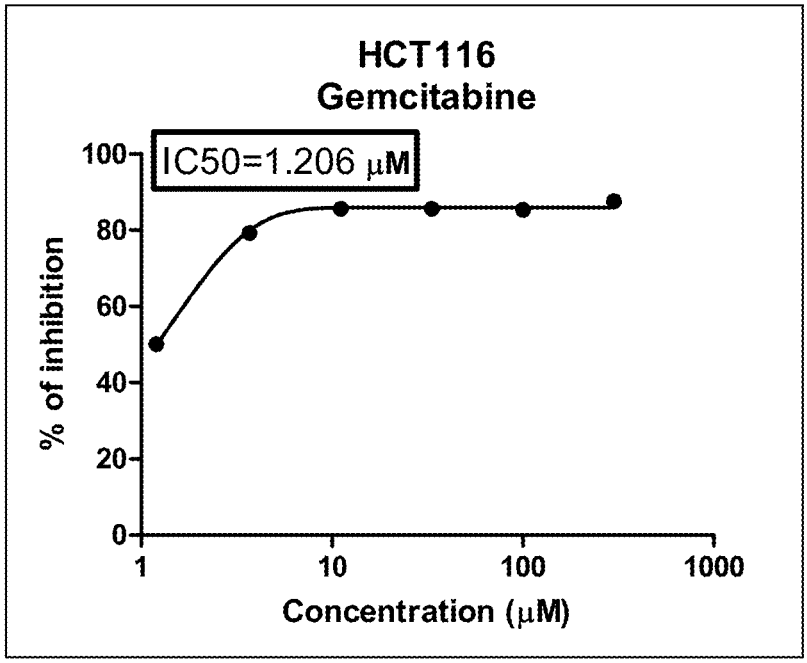

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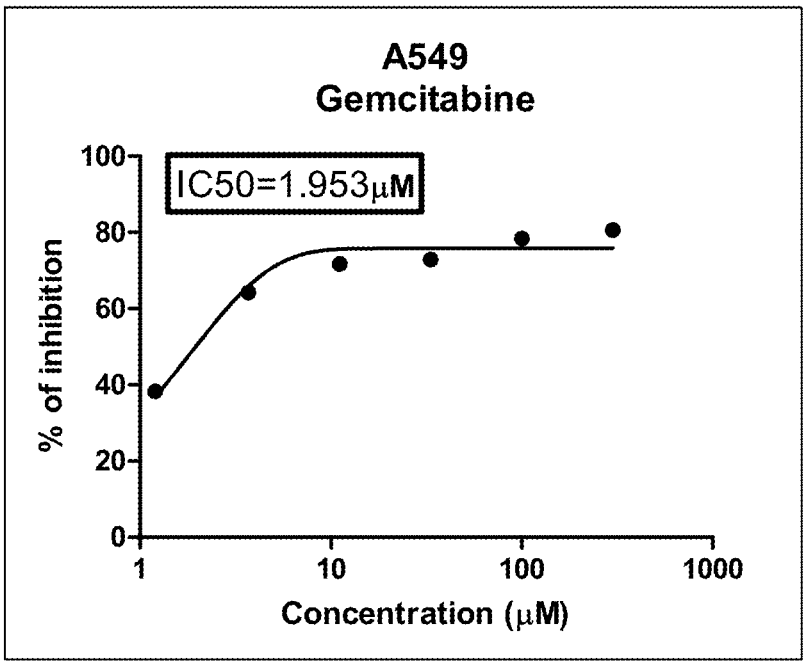

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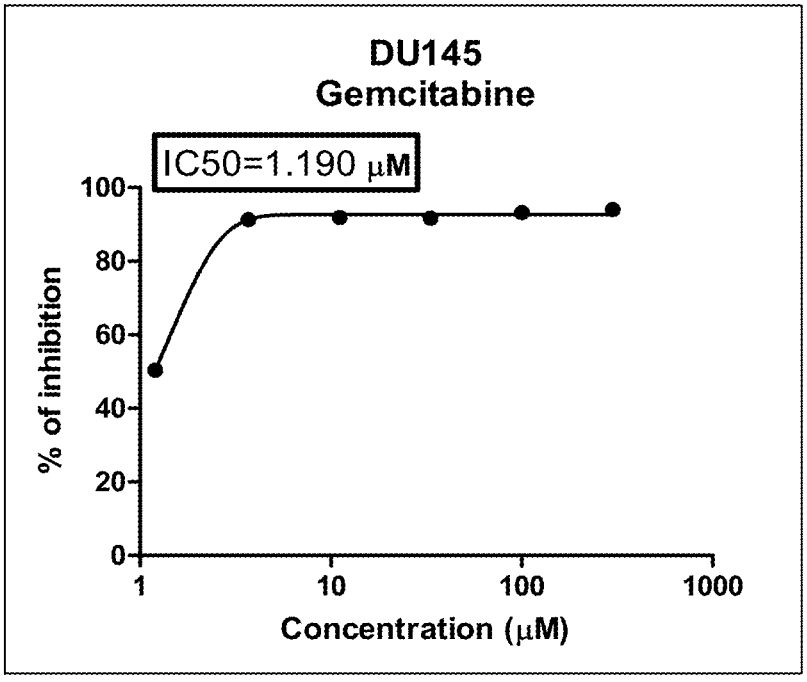


Figure 49

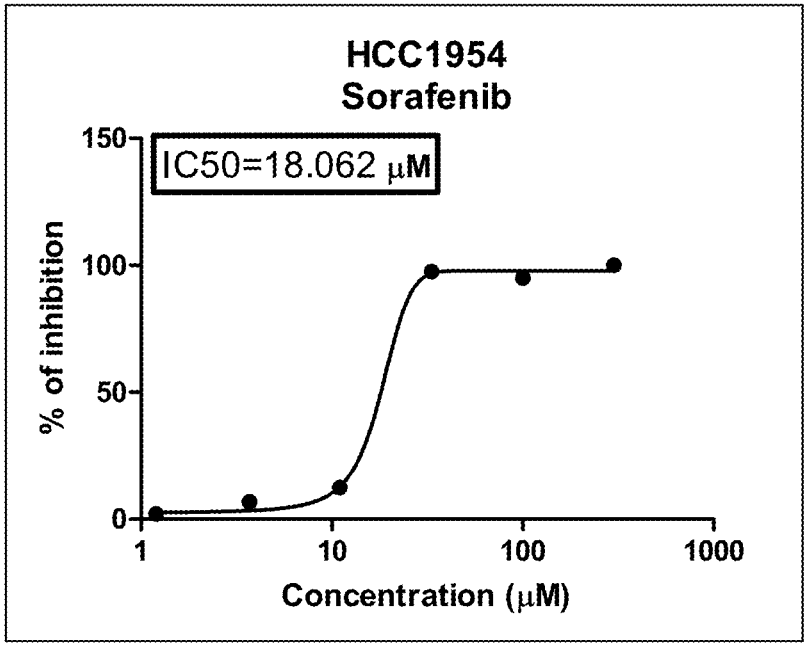


Figure 50

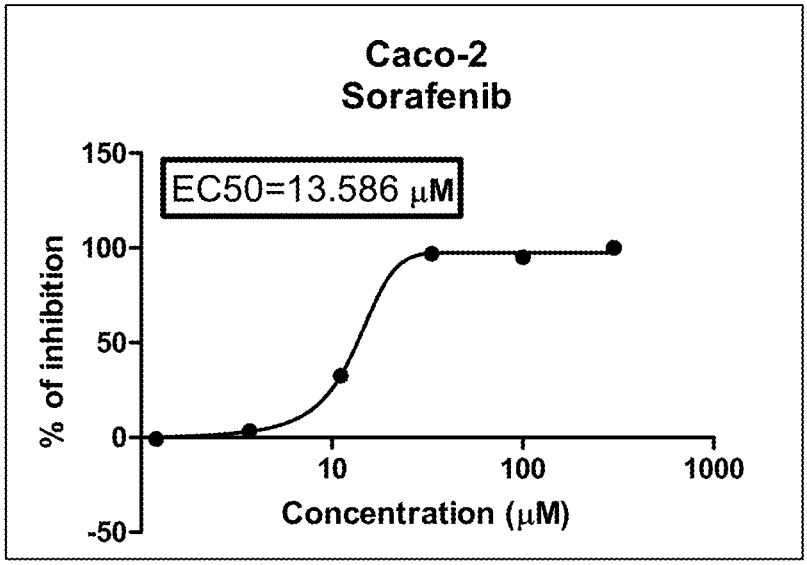
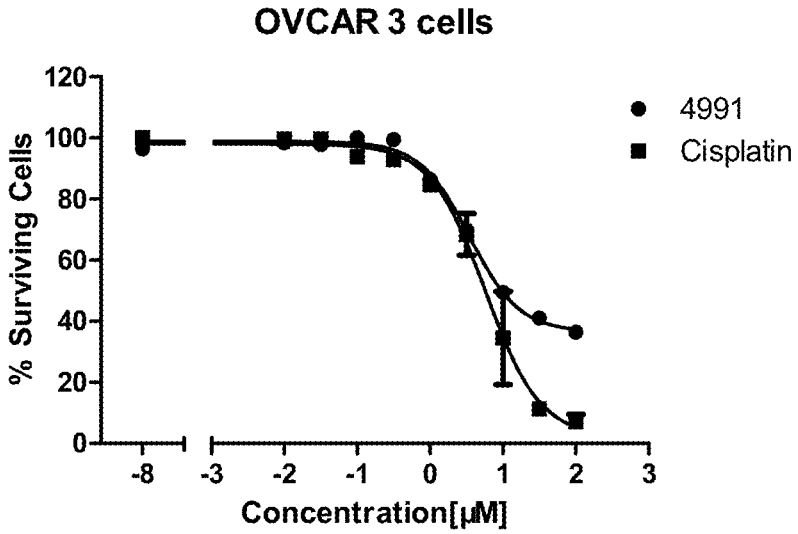
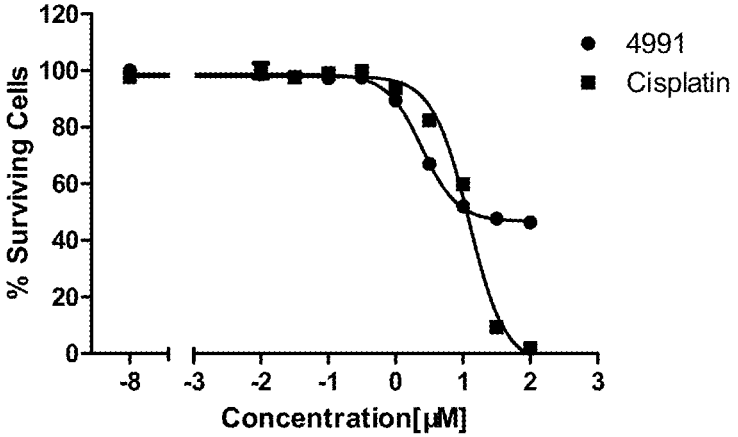


Figure 51



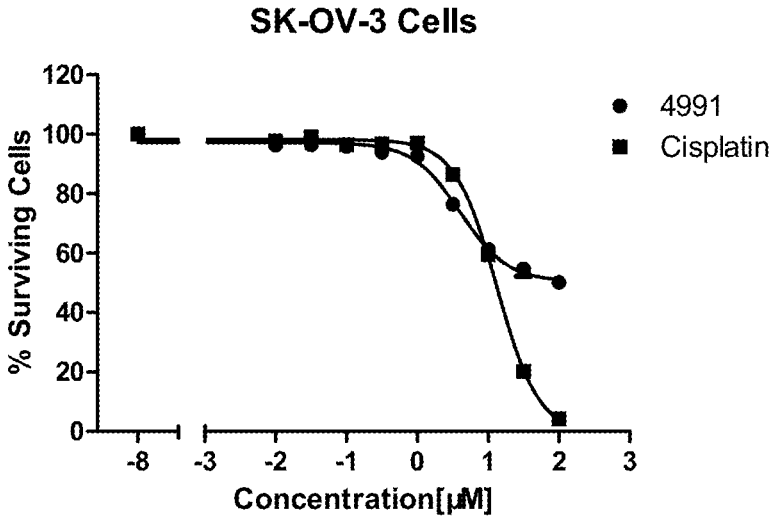
	4991	Cisplatin
IC50	3.475	5.702

Figure 52



	4991	Cisplatin
IC50	2.463	12.24

Figure 53



	4991	Cisplatin
IC50	4.012	13.27

AMINOPYRIMIDINE KINASE INHIBITORS

RELATED APPLICATIONS

This application is a divisional of U.S. patent application Ser. No. 12/978,089 filed Dec. 23, 2010, which claims the benefit of priority to U.S. Provisional Patent Application Ser. No. 61/289,685, filed Dec. 23, 2009; and U.S. Provisional Patent Application Ser. No. 61/324,481, filed Apr. 15, 2010.

BACKGROUND OF THE INVENTION

Casein kinase 1 (CK1) is a family of evolutionarily conserved serine/threonine kinases including seven known members in vertebrates (CK1α, -β, -γ1, -γ2, -γ3, -δ and -ϵ). The CK1s contain a typical kinase domain followed by a C-terminal tail region, which has been implicated in the regulation of CK1 localization, substrate selectivity and kinase activity. Myriad proteins have been found to be phosphorylated by CK1s, which are involved in a wide range of cellular functions including vesicular trafficking, DNA damage repair, cell cycle progression, cytokinesis and circadian rhythms (reviewed by Gross and Anderson (1998); Vielhaber and Virshup (2001); Knippschild et al. (2005)). Moreover, CK1 family members (-α, -δ/ϵ and -γ) modulate the activities of major signaling pathways (for example, Wnt and Shh) through several mechanisms (Peters et al., 1999; Liu et al., 2002; Price and Kalderon, 2002; Davidson et al., 2005; Zeng et al., 2005 and reviewed by Price (2006)).

In mammals seven CK1 isoforms, namely CK1α, γ, $\gamma_{1\text{-}3}$, δ and ϵ, and several splice variants have been described. They all contain a highly conserved kinase domain, a short N-terminal domain of 6 to 76 amino acids and a highly variable C-terminal domain of 24 to more than 200 amino acids. The constitutive phosphotransferase activity of CK1 isoforms is tightly controlled by several mechanisms. For example, the closely related isoforms CK1δ and ϵ, which share a 98% identity at the amino acid level in their catalytic domain, are regulated by autophosphorylation, dephosphorylation and proteolytic cleavage. Members of the CK1 family are found in the nucleus, the cytoplasm and in the plasma membrane. By phosphorylating many different substrates bearing either a canonical or non-canonical consensus sequence they modulate the activity of key regulator proteins involved in many cellular processes such as cell differentiation, cell proliferation, apoptosis, circadian rhythm, chromosome segregation, and vesicle transport.

The Pim kinase family contains three isoforms, Pim-1, Pim-2 and Pim-3, and has recently emerged as targets of interest in oncology and immune regulation. Ongoing studies have identified a role for these proteins in cell survival and proliferation, both functionally and mechanistically, and overexpression has been observed in a number of human cancers and inflammatory states.

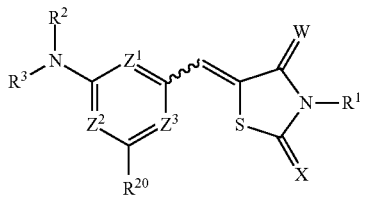
Pim kinases suppress apoptosis and regulate cell-cycle progression. Elevated levels of Pim kinases have been reported in solid tumors such as prostate cancer and pancreatic cancer. Pim-1 was initially discovered in murine leukemia and several independent studies have shown this kinase to be upregulated in human prostate cancer. Pim-1, 2 and 3 make up a distinct and highly homologous family of serine/threonine kinases belonging to the calmodulin-dependent protein kinase-related (CAMK) family. In addition to the three gene-encoded proteins, translational variants have also been reported for Pim-1 and 2 resulting from utilization of alternative start codons. The name Pim refers to the original identification of the pim-1 gene as a frequent proviral insertion site in Moloney murine leukemia virus-induced T-cell lymphomas, and the gene encoding Pim-2 was subsequently found to have similar susceptibility. Pim-3, originally designated kinase induced by depolarization (KID)-1, was later renamed due to high sequence similarity to Pim-1 (71% identity at the amino acid level). Considering all three isoforms, Pim proteins are widely expressed with high levels in hematopoietic tissue and are aberrantly expressed in a variety of human malignancies. Pim kinases positively regulate cell survival and proliferation, affording therapeutic opportunities in oncology. The Pim protein kinases are frequently overexpressed in prostate cancer and certain forms of leukemia and lymphoma.

A role for Pim kinases in immune regulation has also been observed. Pim-2 has been reported to have enhanced levels of expression in a variety of inflammatory states and may function as a positive regulator of interleukin-6 (IL-6), whereby overexpression of the kinase augments stimulus-induced IL-6 levels. Pim-1 and 2 have also been implicated in cytokine-induced T-cell growth and survival. Comparing the sensitivity of stimulated T cells from Pim-1−/−Pim-2−/− mice to wild-type mice following treatment with the immunosuppressant rapamycin, it was found that T-cell activation was significantly impaired by Pim-1/Pim-2 deficiency, suggesting that Pim kinases promote lymphocyte growth and survival through a PI3K/AKT (PKB, protein kinase B)/mammalian target of rapamycin (mTOR)-independent pathway. Other parallel but independent functions and overlapping substrate specificity for proteins in these pathways have been reported as well, including the positive regulation of transcription of nuclear factor kappa-B (NF-κB)-responsive genes, which have implications in both inflammation and oncology. Therefore, Pim kinases are attractive targets for both therapeutic areas. Further, Pim kinases have been reported to play a role in the protection of the ATP-binding cassette (ABC) transporter P-glycoprotein (Pgp; ABCB1) from proteolytic and proteasomal degradation. Pgp is known to mediate drug efflux and as such, inhibitors of Pim kinases may provide a novel approach to abrogating drug resistance.

SUMMARY OF THE INVENTION

An aspect of the present invention relates to compounds that inhibit casein kinase 1 and/or casein kinase 2 and/or a PIM kinase. For example, an embodiment relates to a compound of formula 1:

1



or a pharmaceutically acceptable salt thereof, wherein independently for each occurrence:

W and X are independently oxygen or sulfur;

Z^1, Z^2 and Z^3 are independently C—R^{20} or N, provided that at least one of Z^1 and Z^2 is N;

R^1 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl, heterocyclyl, aralkyl,

heteroaralkyl, heterocyclylalkyl, —COR^6, —$C(O)OR^6$, —$SO_2(R^6)$, —$C(O)N(R^6)(R^7)$, —$SO_2N(R^6)(R^7)$, and —$[C(R^4)_2]_p$—R^5;

R^2 and R^3 are each independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl, heterocyclyl, aralkyl, heteroaralkyl, heterocyclylalkyl, —$[C(R^4)_2]_p$—R^5, —COR^6, —$C(O)OR^6$, —$SO_2(R^6)$, —$C(O)_N(R^6)(R^7)$, —$SO_2N(R^6)(R^7)$, —$P(O)(OR^6)(OR^7)$; or R^2 and R^3 are joined together to form an optionally substituted heterocyclic ring;

R^4 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, heterocyclylalkyl, aralkyl, heteroaryl, heteroaralkyl, halo, hydroxy, alkoxy, hydroxyalkyl, and alkoxyalkyl;

R^5 is selected from the group consisting of aryl, heteroaryl, heterocyclyl, —$N(R^8)(R^9)$, —$N(R^8)COR^9$, —$N(R^8)C(O)OR^9$, —$N(R^8)SO_2(R^9)$, —$CON(R^8)(R^9)$, —$OC(O)N(R^8)$—(R^9), —$SO_2N(R^8)(R^9)$, —$OC(O)OR^8$, —$COOR^9$, —$C(O)N(OH)(R^8)$, —$OS(O)_2OR^8$, —$S(O)_2OR^8$, —$S(O)_2R^8$, —OR^8, —COR^8, —$OP(O)(OR^8)(OR^8)$, —$P(O)(OR^8)(OR^8)$ and —$N(R^8)P(O)(OR^9)(OR^9)$;

R^6 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl, heterocyclyl, aralkyl, heteroaralkyl, and heterocyclylalkyl;

R^7 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl, heterocyclyl, aralkyl, heteroaralkyl, and heterocyclylalkyl; or R^6 and R^7 are joined together to form a heterocyclic ring;

R^8 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl, heterocyclyl, aralkyl, heteroaralkyl, and heterocyclylalkyl;

R^9 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl, heterocyclyl, aralkyl, heteroaralkyl, and heterocyclylalkyl; or R^8 and R^9 are joined together to form a heterocyclic ring;

R^{20} is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl, heterocyclyl, aralkyl, heteroaralkyl, heterocyclylalkyl, halo, haloalkyl, trifluoromethyl, fluoroalkyl, perfluoroalkyl, thio, cyano, hydroxy, methoxy, alkoxy, phenoxy, aryloxy, heteroaryloxy, carboxyl, alkoxycarbonyl, acyl, nitro, amino, alkylamino, arylamino, heteroarylamino, amido, acylamino, sulfate, sulfonate, sulfonyl, sulfoxido, sulfonamido, sulfamoyl, —$[C(R^4)_2]_p$—R^5, $NR^{14}R^{15}$, OR^{16}, O—$[C(R^4)_2]_p$—R^5, NR^{14}—$[C(R^4)_2]_p$—R^5 and SR^{16};

R^{14} and R^{15} are each independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl, heterocyclyl, aralkyl, heteroaralkyl, heterocyclylalkyl, —$[C(R^4)_2]_p$—R^5, —COR^6, —$C(O)OR^6$, —$SO_2(R^6)$, —$C(O)N(R^6)(R^7)$, —$SO_2N(R^6)(R^7)$, and —$P(O)(OR^6)(OR^7)$; or R^{14} and R^{15} are joined together to form an optionally substituted heterocyclic ring;

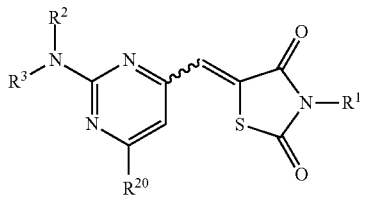
R^{16} is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl, heterocyclyl, aralkyl, heteroaralkyl, heterocyclylalkyl, —$[C(R^4)_2]_p$—R^5, —COR^6, and —$C(O)N(R^6)(R^7)$; and

p is 1, 2, 3, 4, 5, or 6;

wherein any one of the aforementioned alkyl, alkenyl, alkynyl, aryl, heteroaryl, heterocyclyl, aralkyl, heteroaralkyl, and heterocyclylalkyl may be optionally substituted.

An embodiment relates to a compound of formula 2:

2



or a pharmaceutically acceptable salt thereof, wherein independently for each occurrence:

R^1 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl, heterocyclyl, aralkyl, heteroaralkyl, heterocyclylalkyl, —COR^6, —$C(O)OR^6$, —$SO_2(R^6)$, —$C(O)_N(R^6)(R^7)$, —$SO_2N(R^6)(R^7)$, and —$[C(R^4)_2]_p$—R^5;

R^2 and R^3 are each independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl, heterocyclyl, aralkyl, heteroaralkyl, heterocyclylalkyl, —$[C(R^4)_2]_p$—R^5, —COR^6, —$C(O)OR^6$, —SOAR), —$C(O)N(R^6)(R^7)$, —$SO_2N(R^6)(R^7)$—$P(O)(OR^6)(OR^7)$; or R^2 and R^3 are joined together to form an optionally substituted heterocyclic ring;

R^4 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, heterocyclylalkyl, aralkyl, heteroaryl, heteroaralkyl, halo, hydroxy, alkoxy, hydroxyalkyl, and alkoxyalkyl;

R^5 is selected from the group consisting of aryl, heteroaryl, heterocyclyl, —$N(R^8)(R^9)$, —$N(R^8)COR^9$, —$N(R^8)C(O)OR^9$, —$N(R^8)SO_2(R^9)$, —$CON(R^8)(R^9)$, —$OC(O)N(R^8)$—(R^9), —$SO_2N(R^8)(R^9)$, —$OC(O)OR^8$, —$COOR^S$, —$C(O)N(OH)(R^8)$, —$OS(O)_2OR^8$, —$S(O)_2OR^8$, —$S(O)_2R^8$, —OR^8, —COR^8, —$OP(O)(OR^8)(OR^9)$, —$P(O)(OR^8)(OR^9)$ and —$N(R^8)P(O)(OR^9)(OR^9)$;

R^6 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl, heterocyclyl, aralkyl, heteroaralkyl, and heterocyclylalkyl;

R^7 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl, heterocyclyl, aralkyl, heteroaralkyl, and heterocyclylalkyl, or R^6 and R^7 are joined together to form a heterocyclic ring;

R^8 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl, heterocyclyl, aralkyl, heteroaralkyl, and heterocyclylalkyl;

R^9 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl, heterocyclyl, aralkyl, heteroaralkyl, and heterocyclylalkyl; or R^8 and R^9 are joined together to form a heterocyclic ring;

R^{20} is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl, heterocyclyl, aralkyl, heteroaralkyl, heterocyclylalkyl, halo, haloalkyl, trifluoromethyl, fluoroalkyl, perfluoroalkyl, thio, cyano, hydroxyl, methoxy, alkoxy, phenoxy, aryloxy, heteroaryloxy, carboxyl, alkoxycarbonyl, acyl, nitro, amino, alkylamino, arylamino, heteroarylamino, amido, acylamino, sulfate, sulfonate, sulfonyl, sulfoxido, sulfonamido, sulfamoyl, —$[C(R^4)_2]_p$—R^5; $NR^{14}R^{15}$, OR^{16}, and SR^{16};

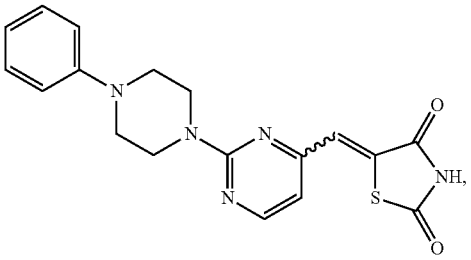
R^{14} and R^{15} are each independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl, heterocyclyl, aralkyl, heteroaralkyl, heterocyclylalkyl, —$[C(R^4)_2]_p$—R^5, —COR^6, —$C(O)OR^6$, —$SO_2(R^6)$, —$C(O)_N(R^6)(R^7)$, —$SO_2N(R^6)(R^7)$, and —$P(O)(OR^6)(OR^7)$; or R^{14} and R^{15} are joined together to form an optionally substituted heterocyclic ring;

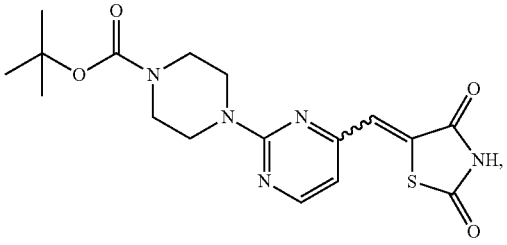
R^{16} is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl, heterocyclyl, aralkyl, heteroaralkyl, heterocyclylalkyl, —$[C(R^4)_2]_p$—R^5, —COR^6, and —$C(O)N(R^6)(R^7)$; and

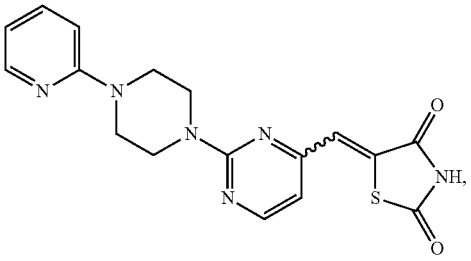
p is 1, 2, 3, 4, 5, or 6;

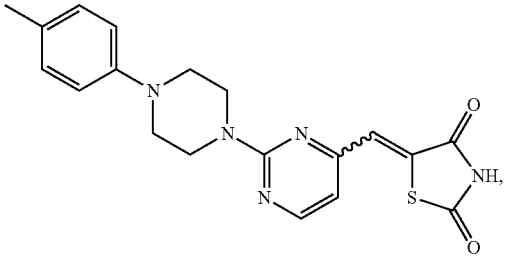
wherein any one of the aforementioned alkyl, alkenyl, alkynyl, aryl, heteroaryl, heterocyclyl, aralkyl, heteroaralkyl, and heterocyclylalkyl may be optionally substituted.

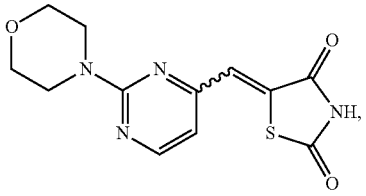
An aspect of the invention relates to a compound, or a pharmaceutically acceptable salt thereof, selected from the group consisting of:











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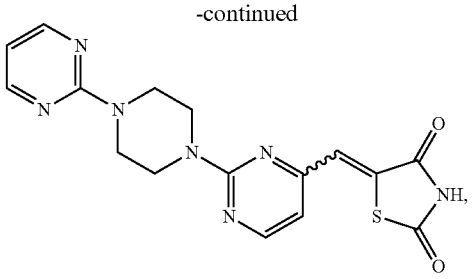

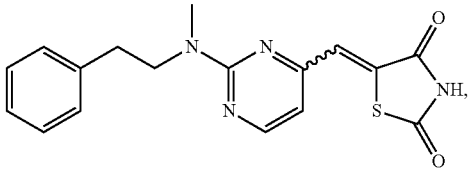

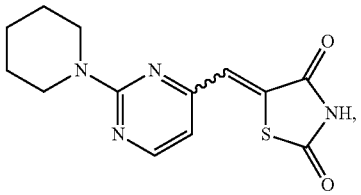

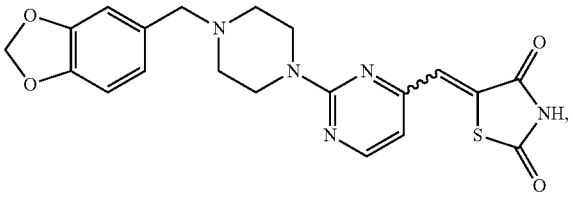

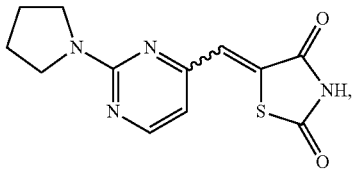

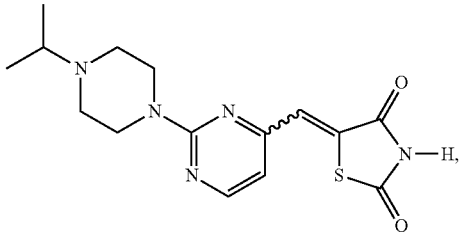

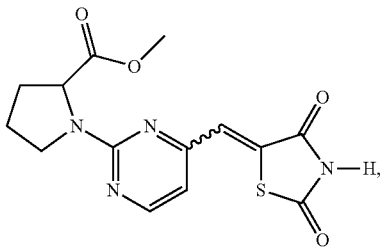

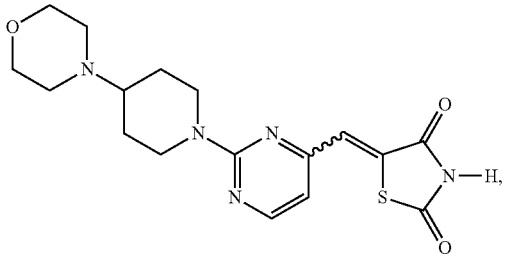

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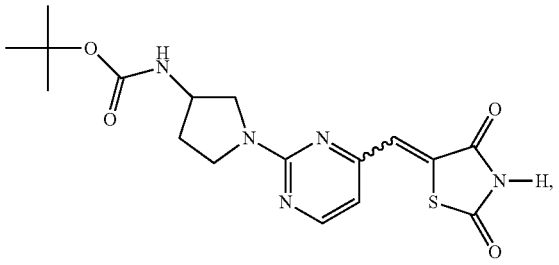

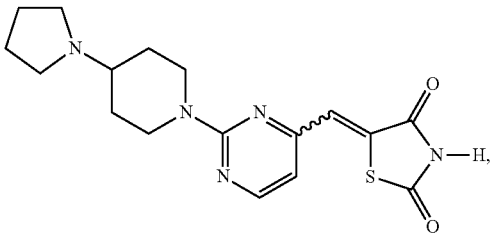

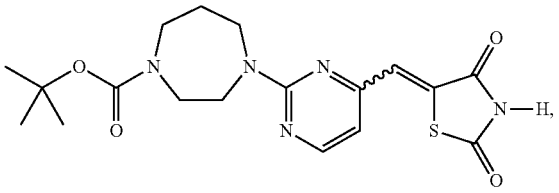

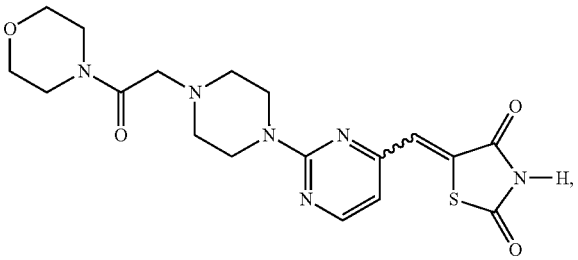

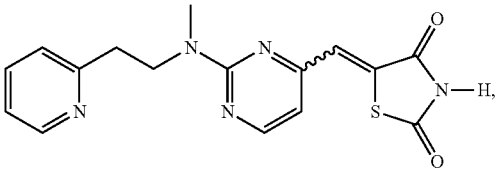

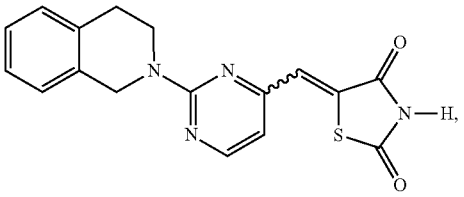

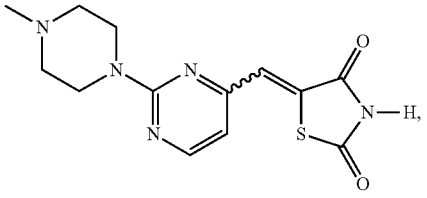

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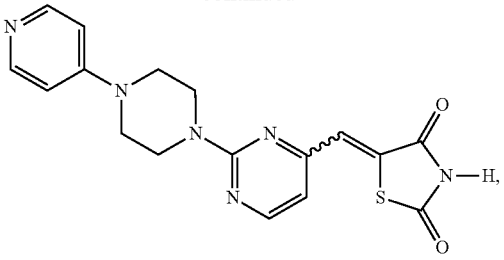

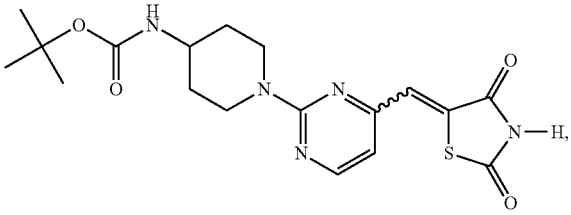

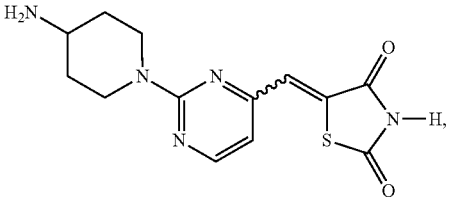

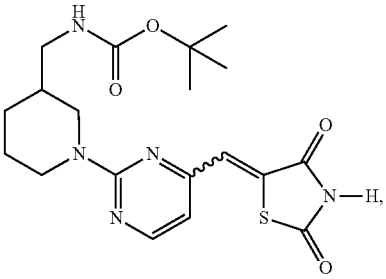

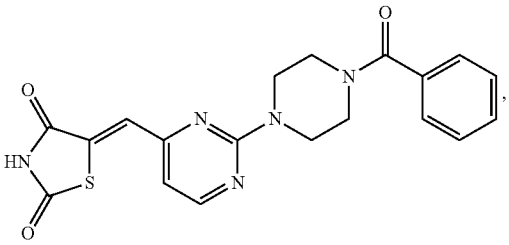

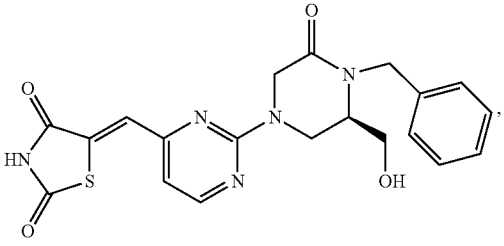

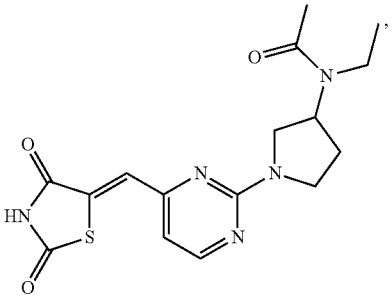

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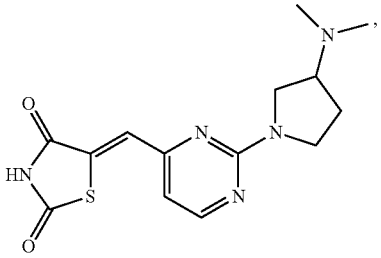

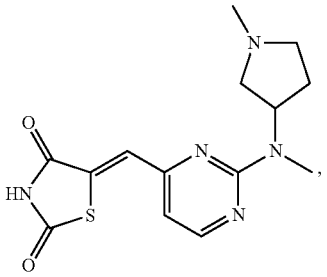

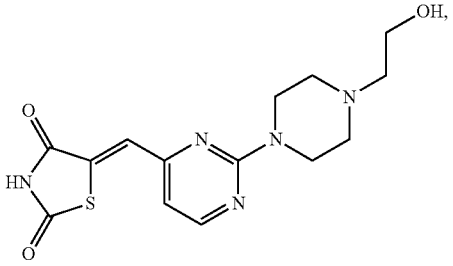

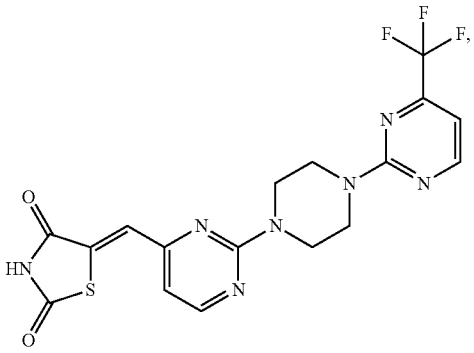

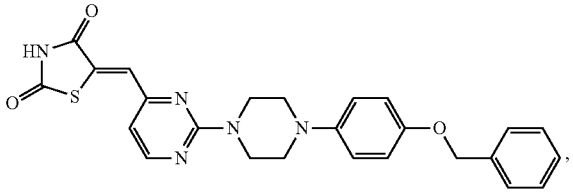

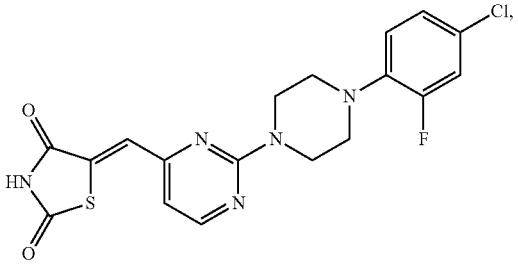

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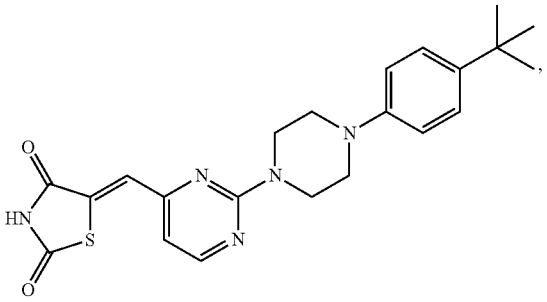

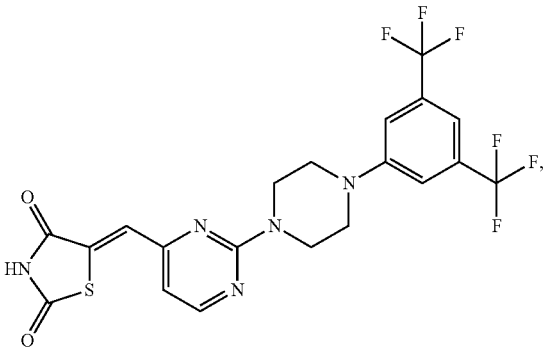

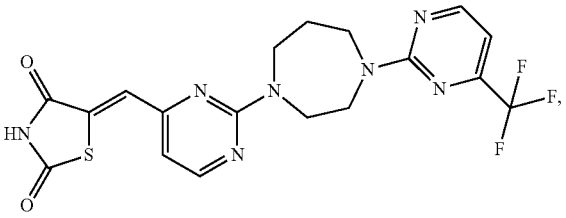

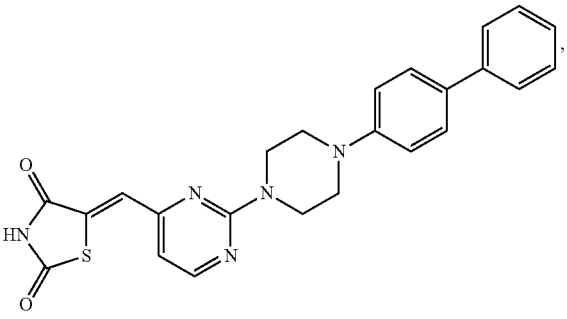

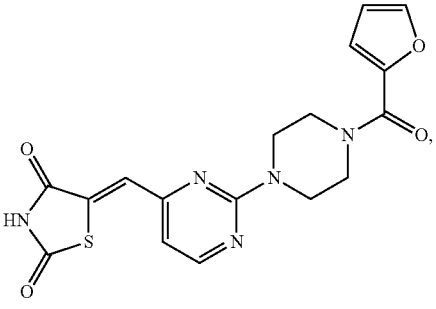

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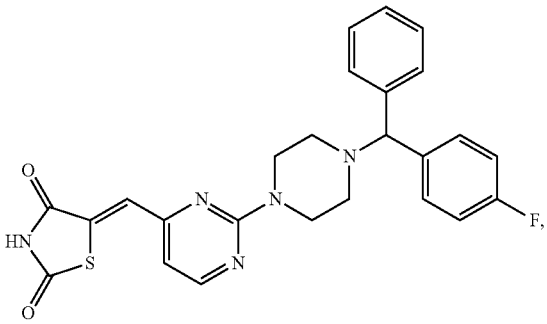

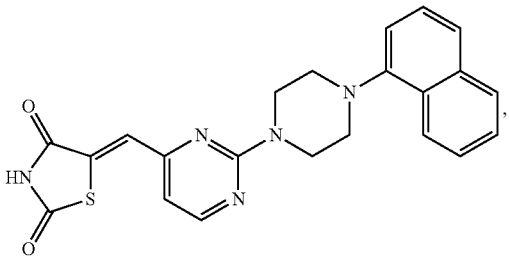

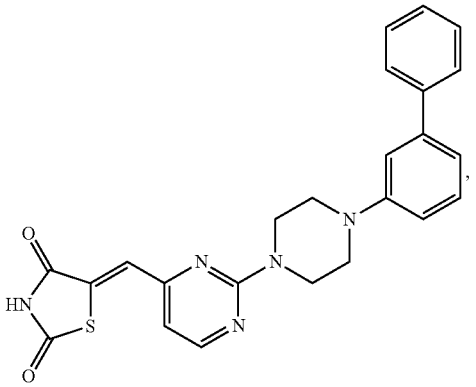

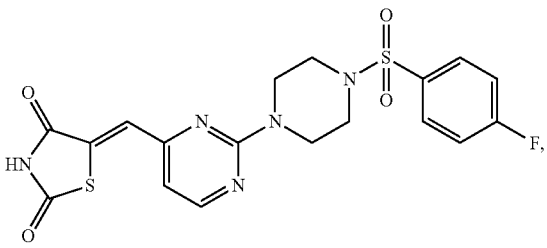

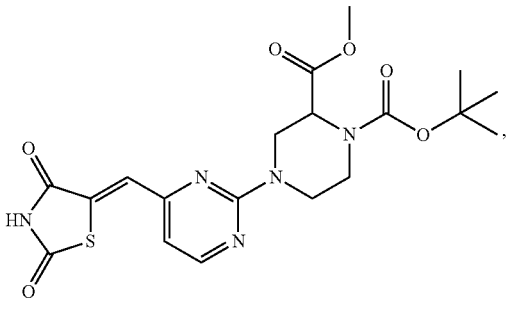

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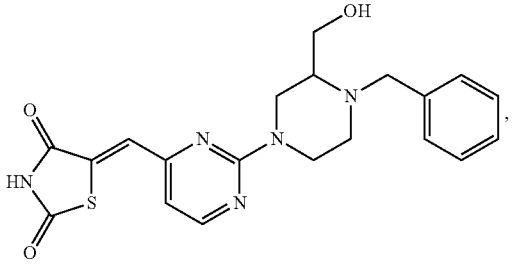

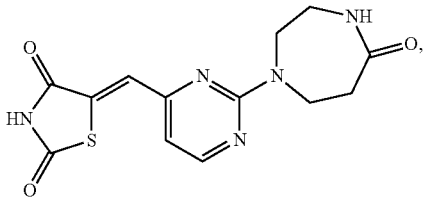

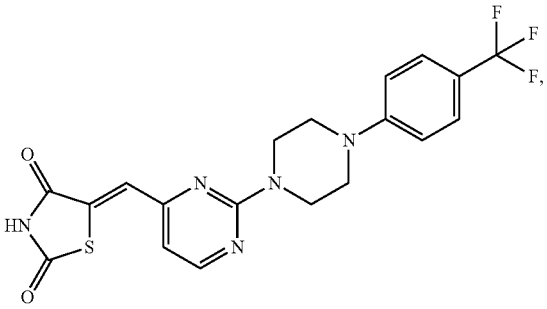

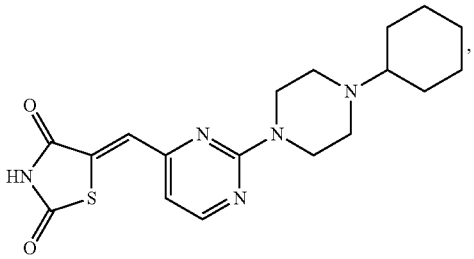

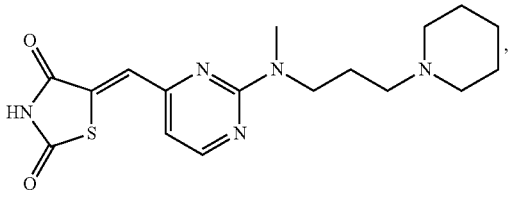

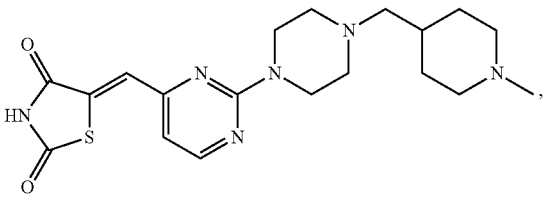

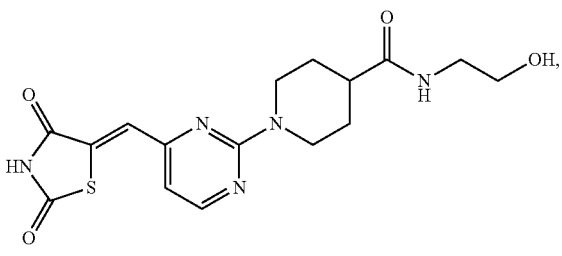

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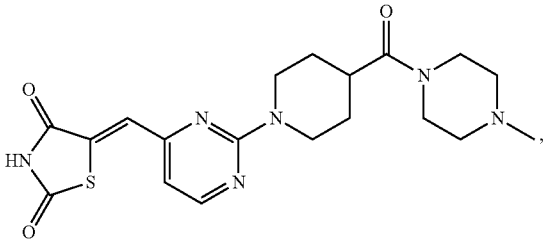

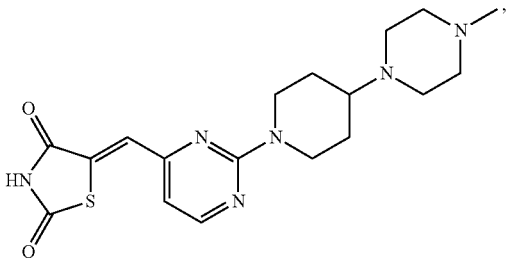

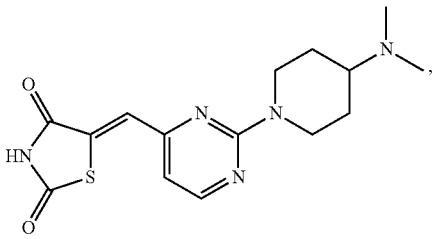

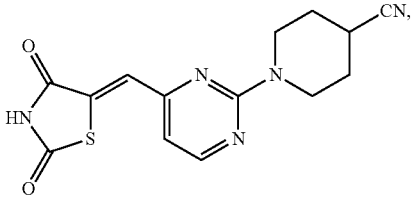

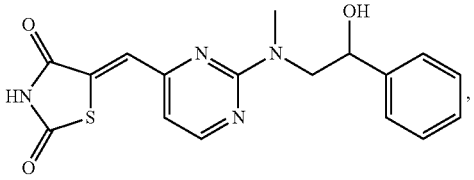

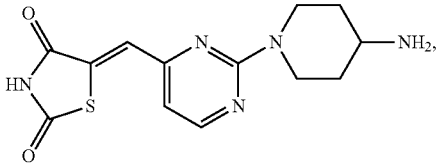

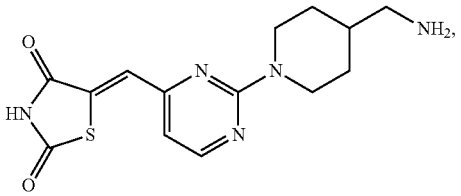

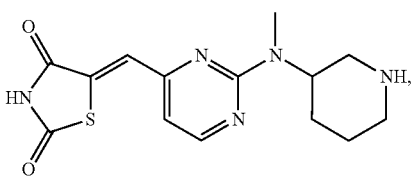

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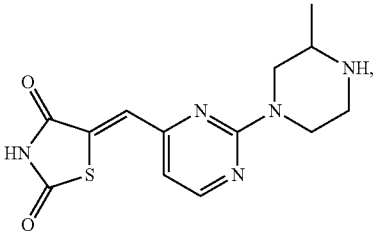

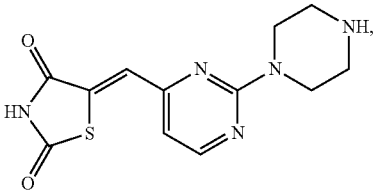

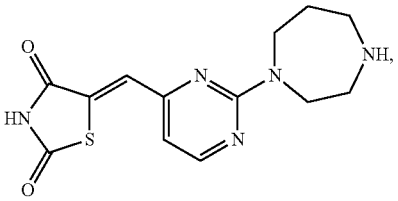

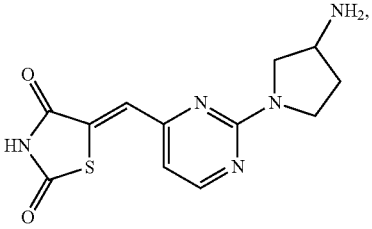

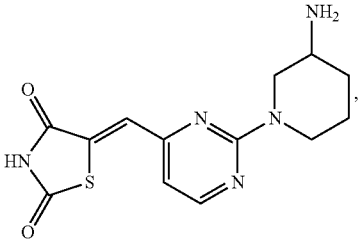

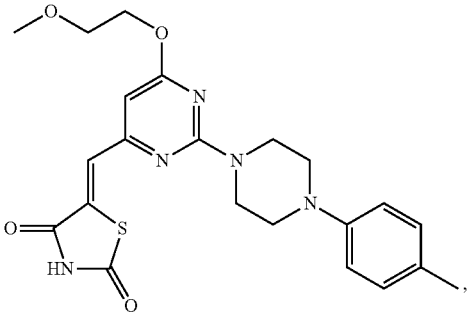

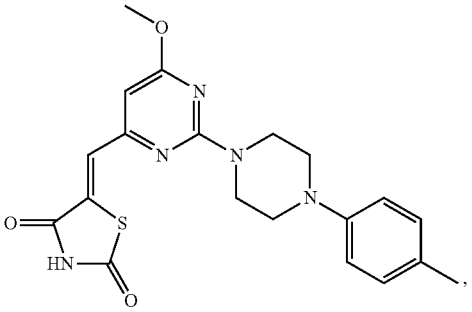

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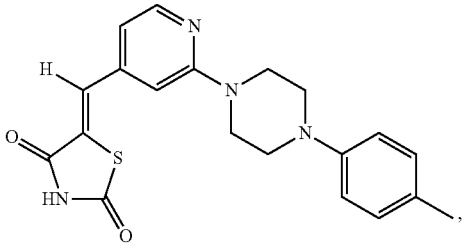

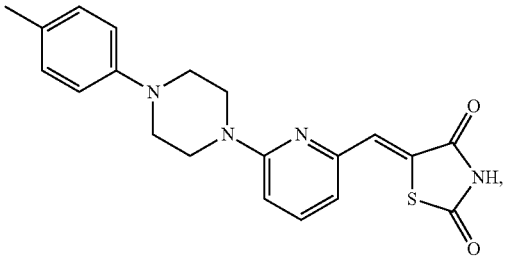

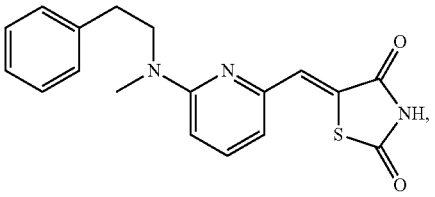

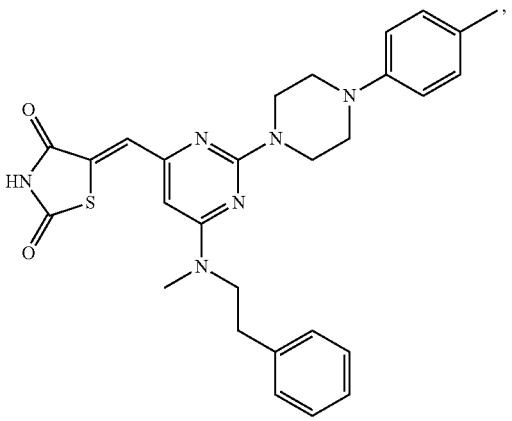

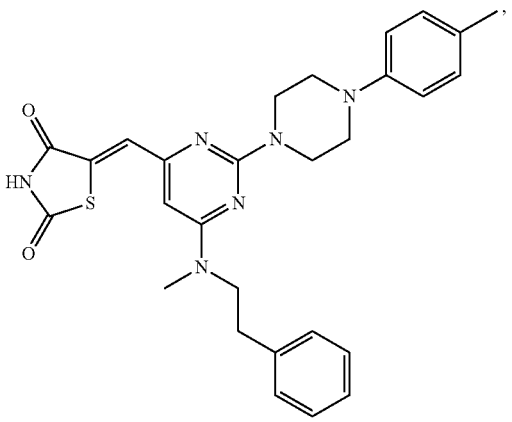

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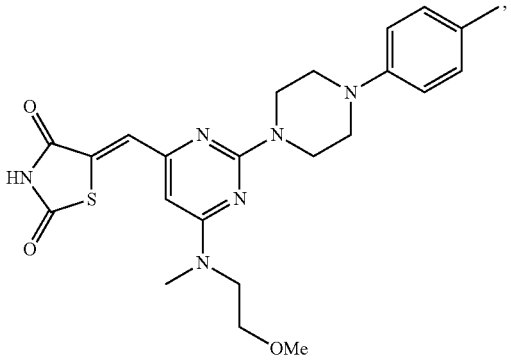

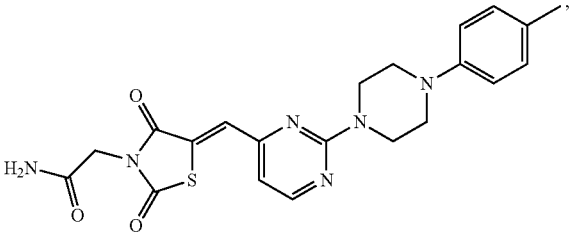

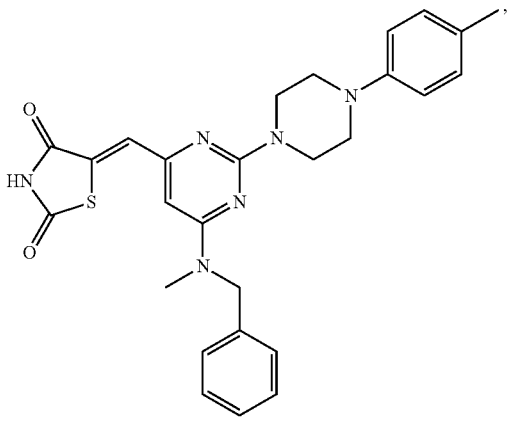

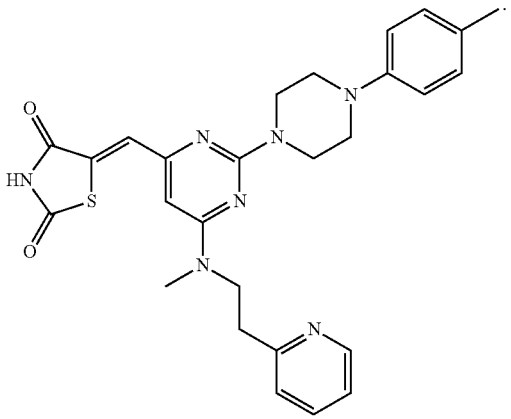

An aspect of the invention relates to a compound, or a pharmaceutically acceptable salt thereof, selected from the group consisting of:

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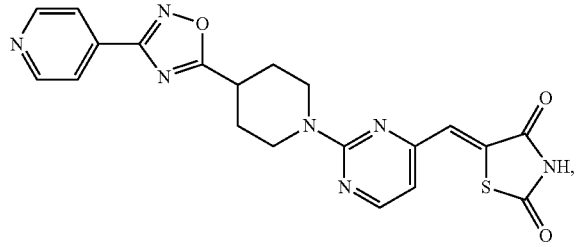

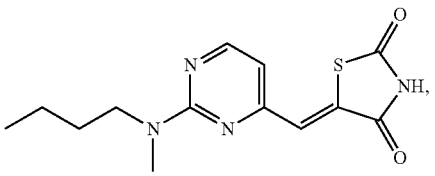

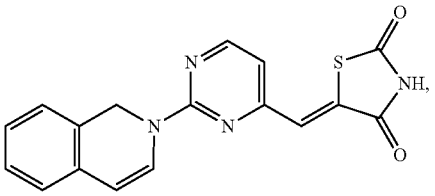

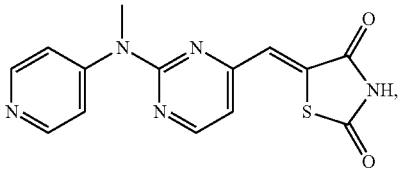

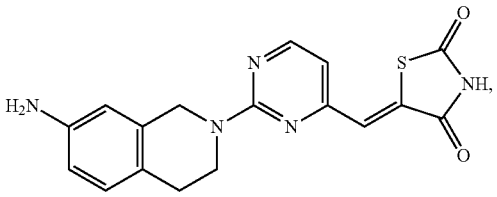

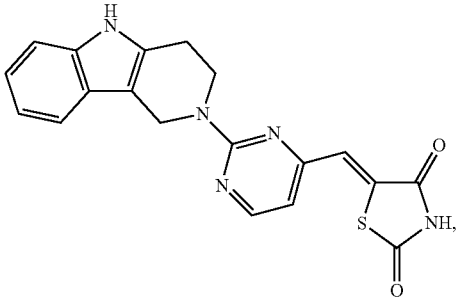

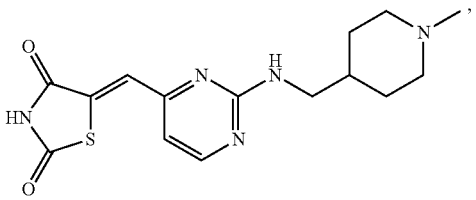

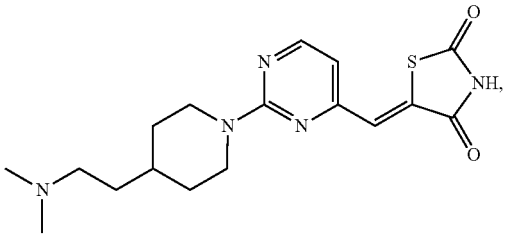

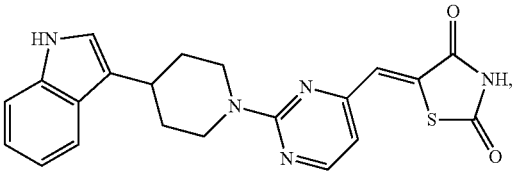

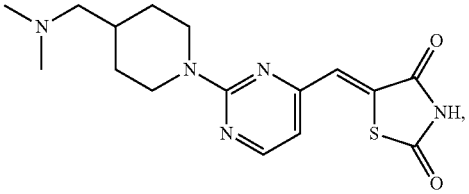

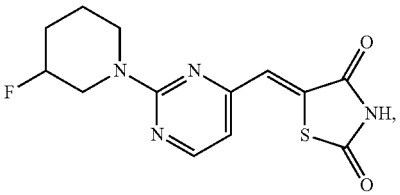

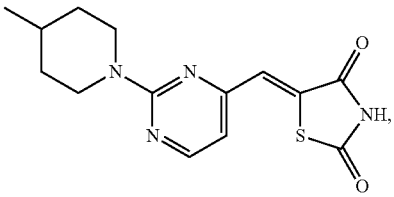

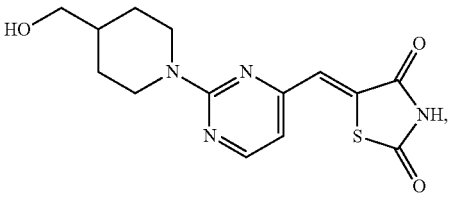

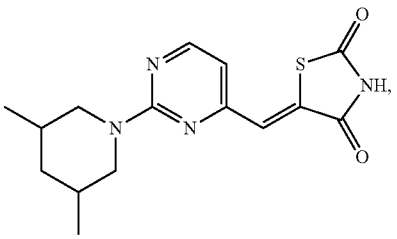

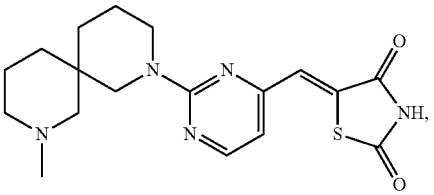

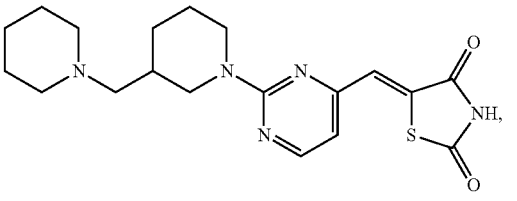

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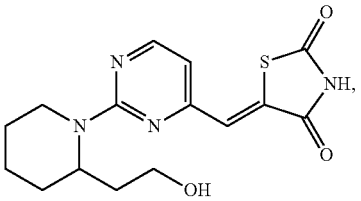

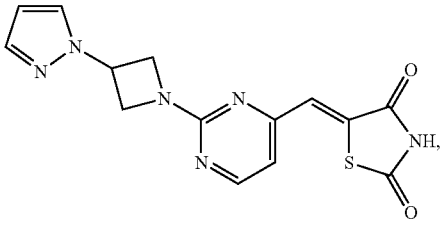

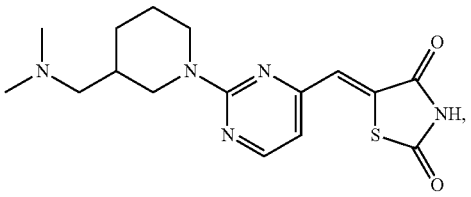

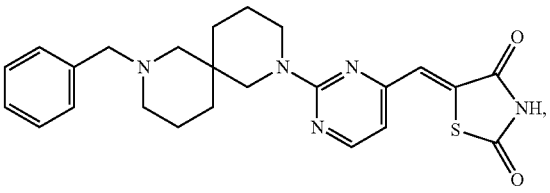

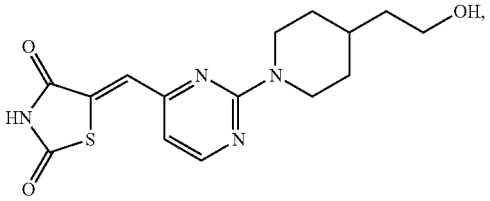

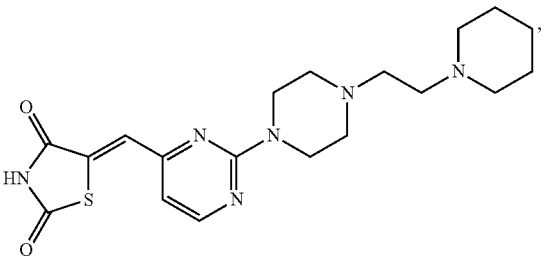

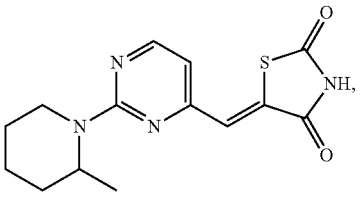

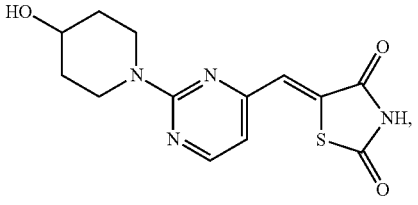

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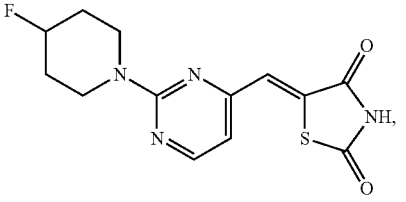

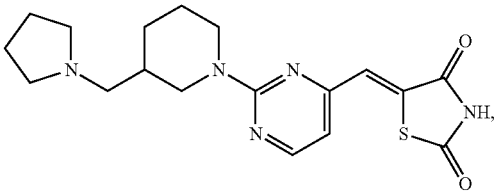

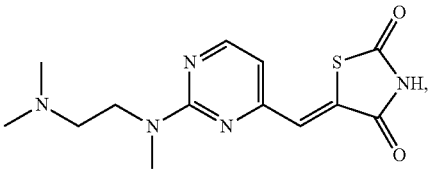

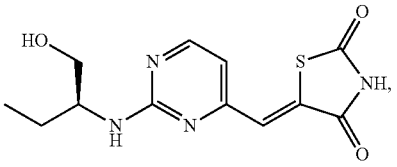

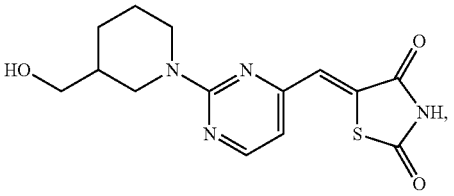

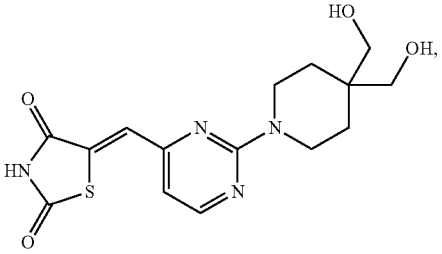

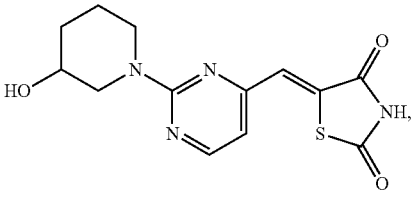

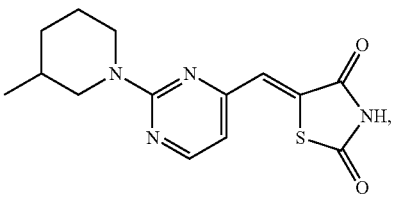

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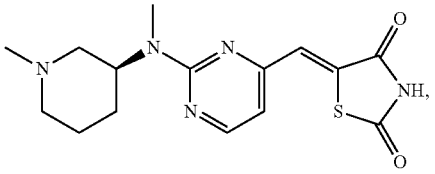

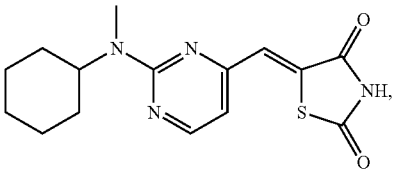

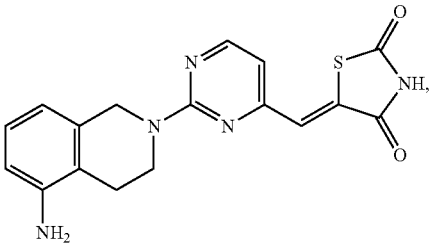

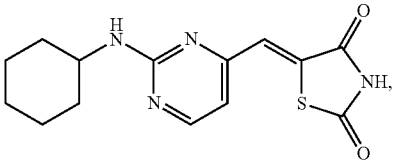

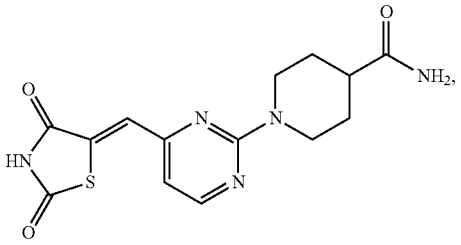

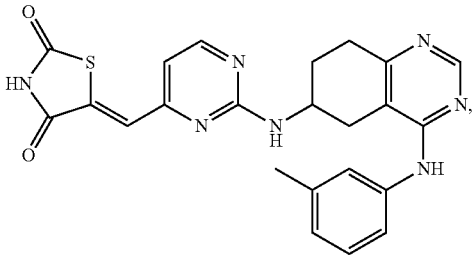

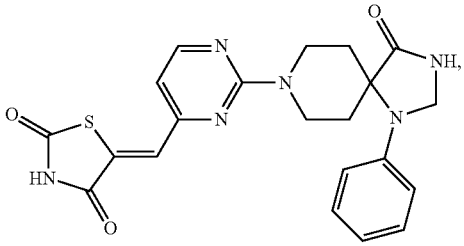

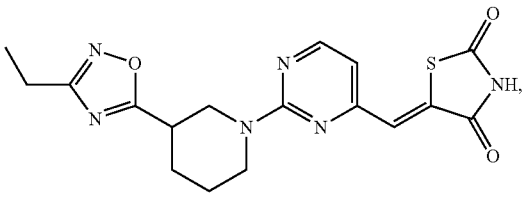

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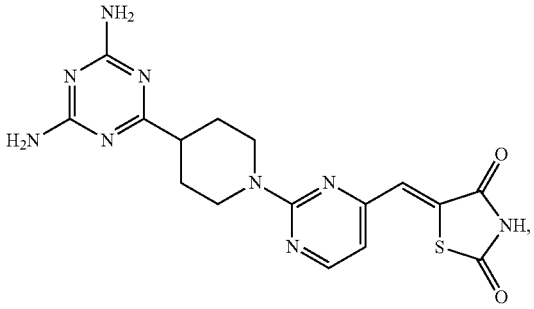

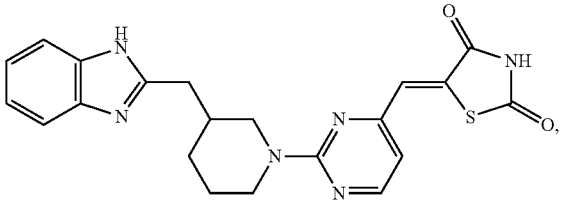

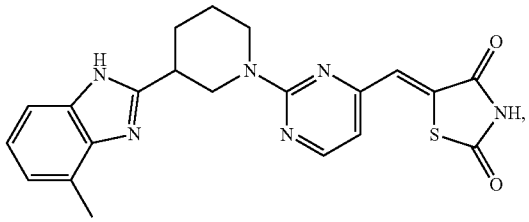

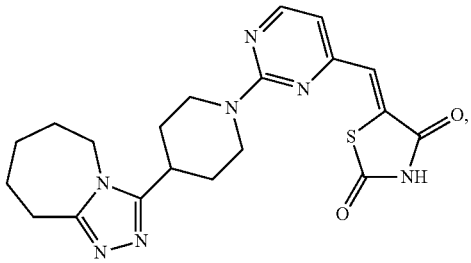

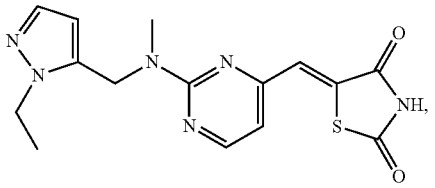

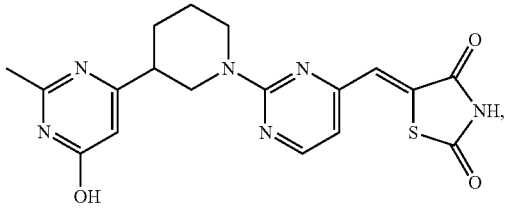

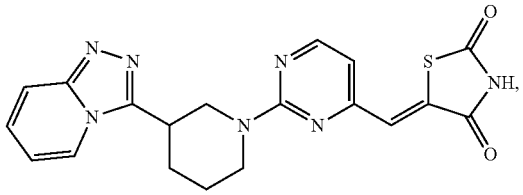

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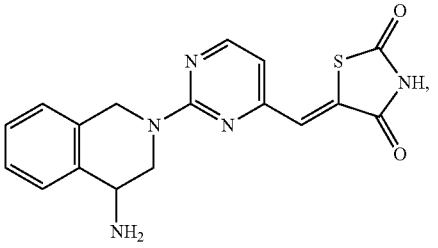

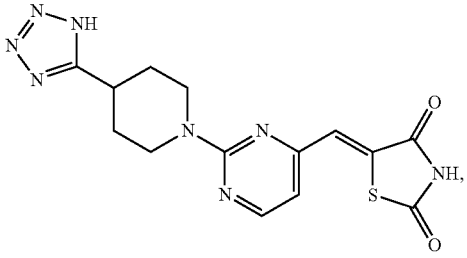

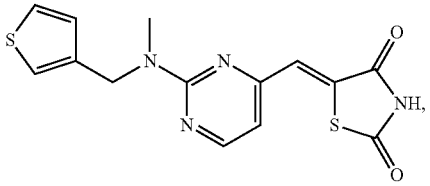

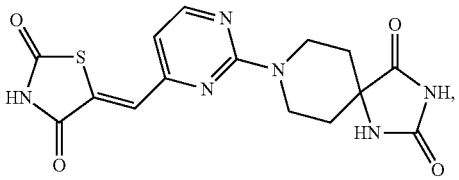

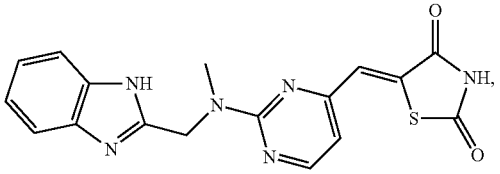

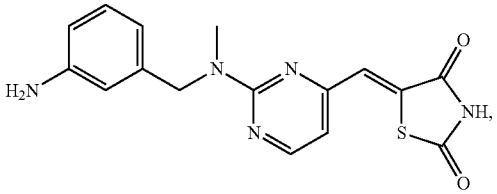

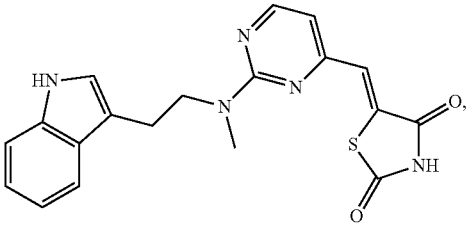

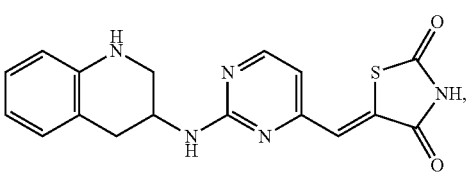

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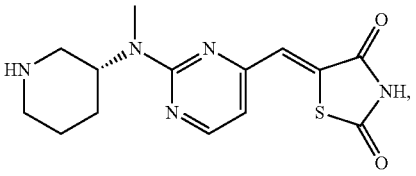

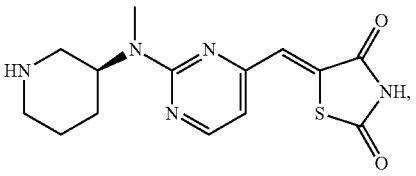

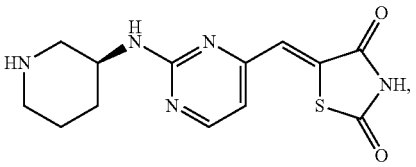

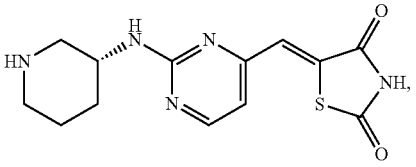

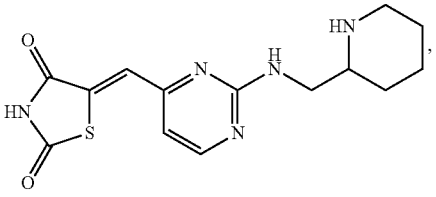

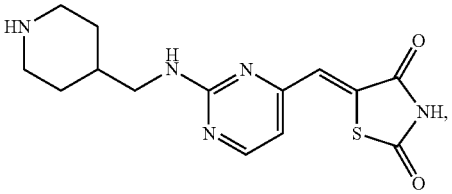

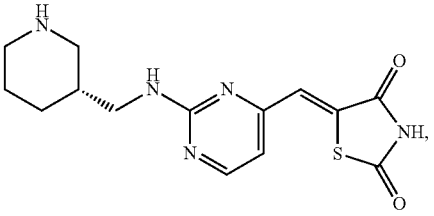

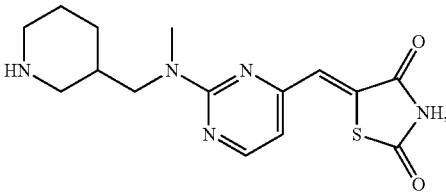

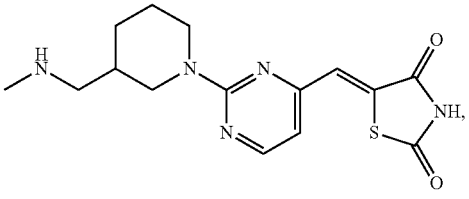

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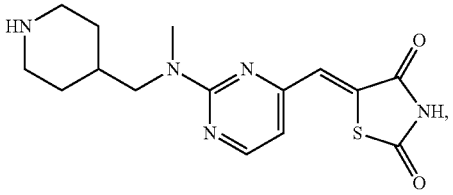

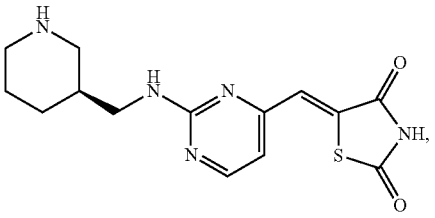

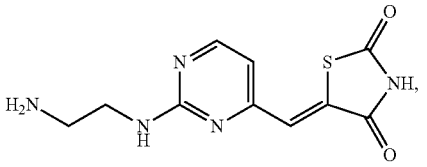

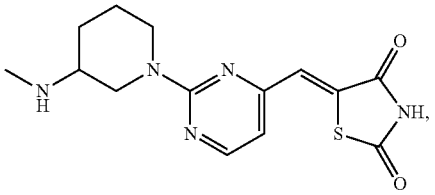

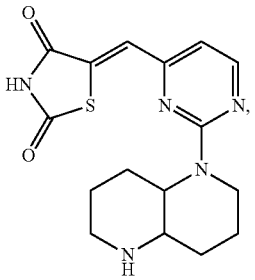

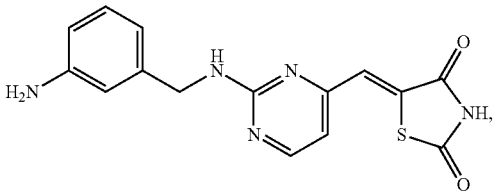

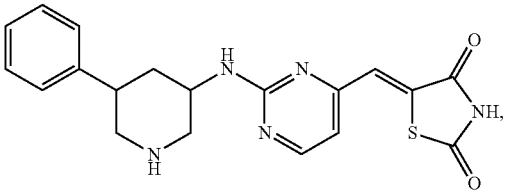

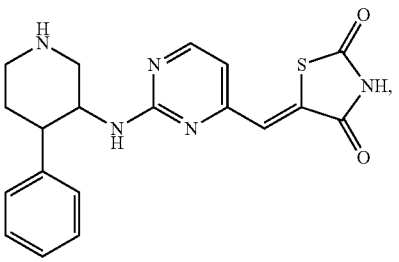

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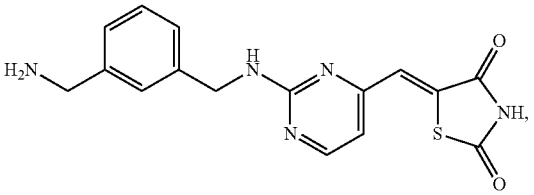

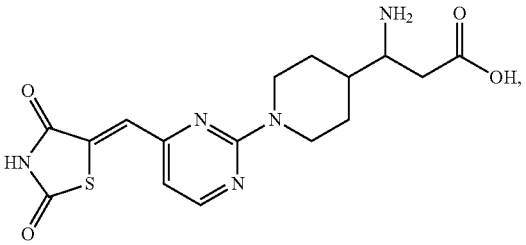

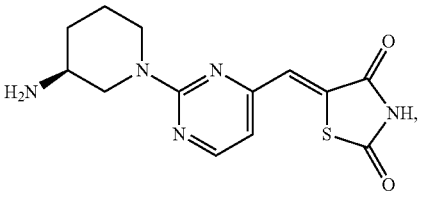

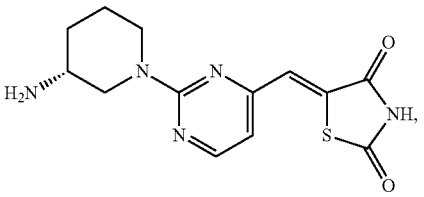

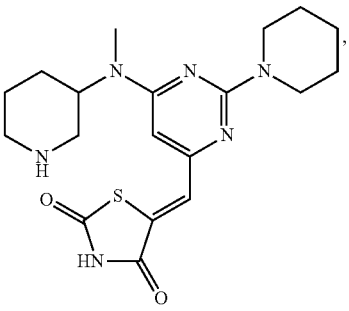

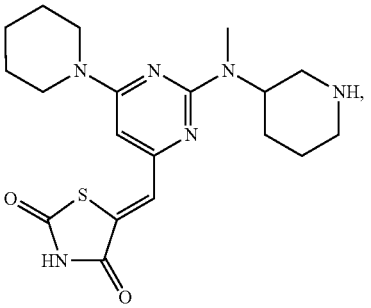

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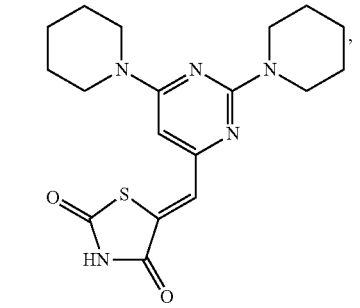

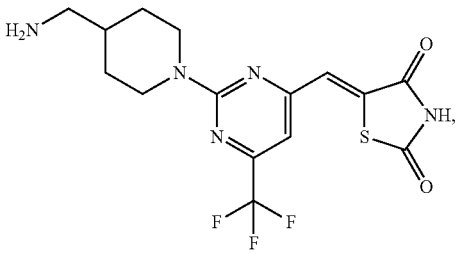

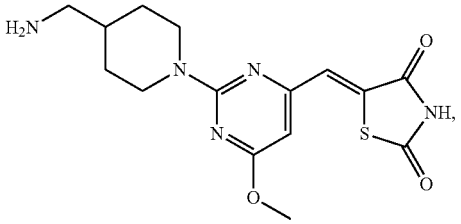

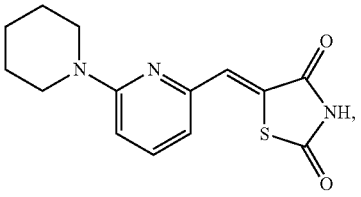

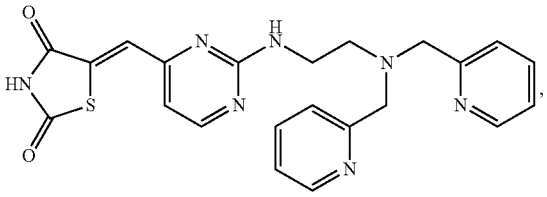

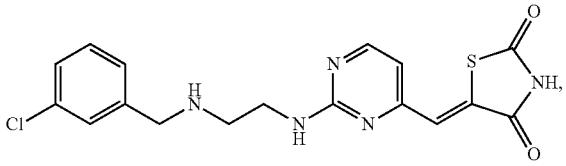

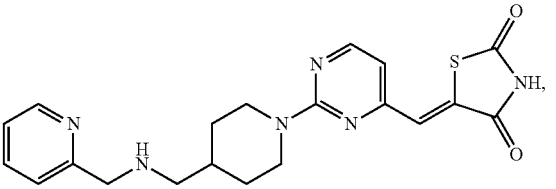

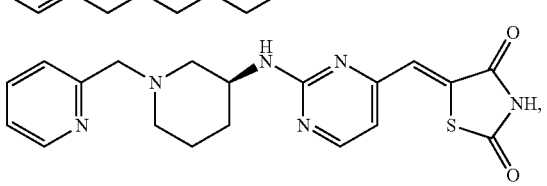

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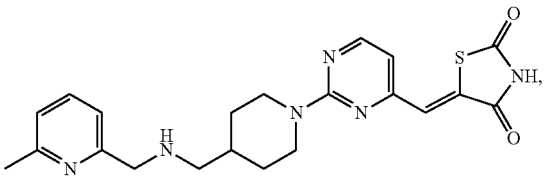

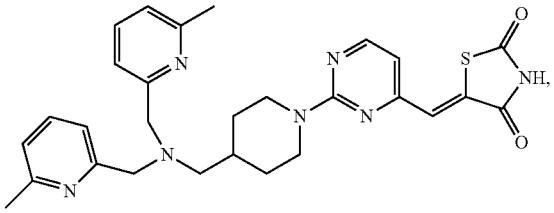

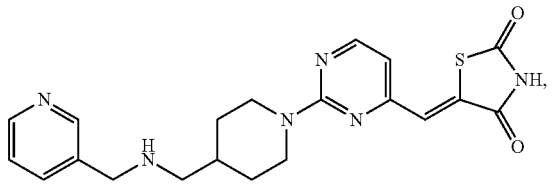

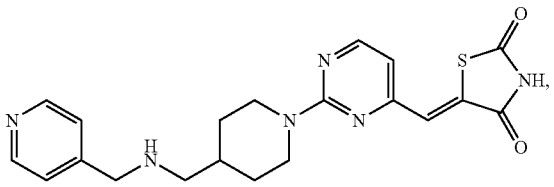

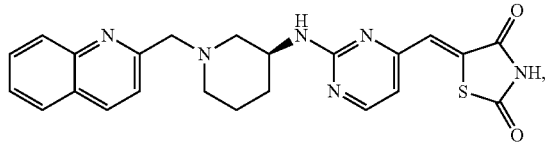

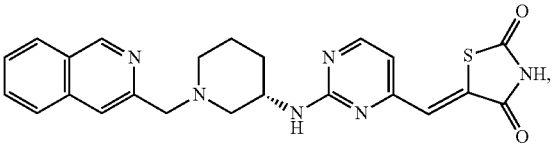

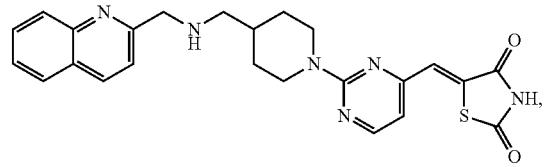

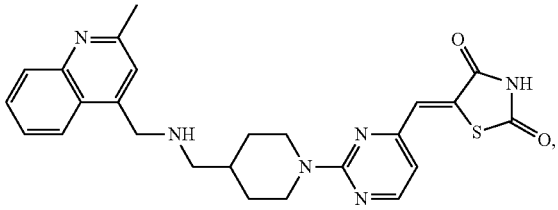

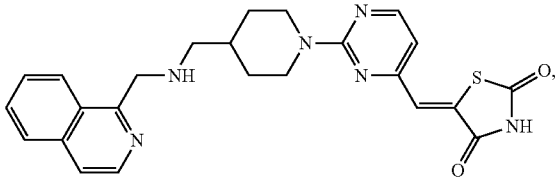

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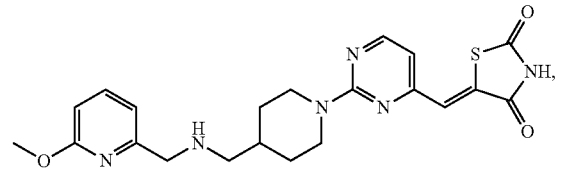

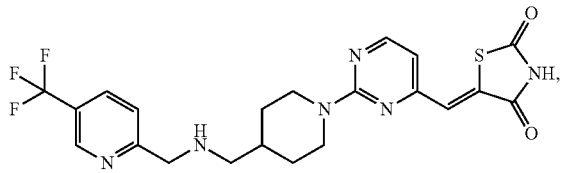

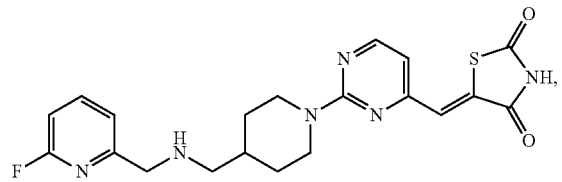

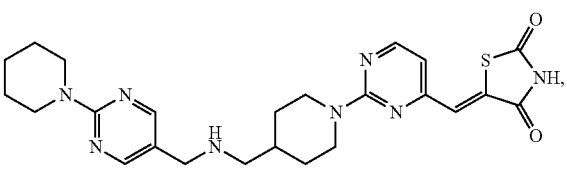

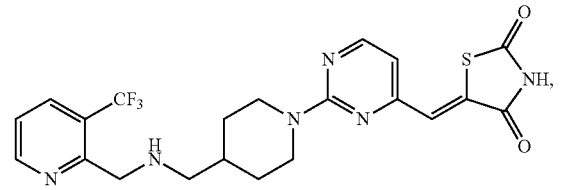

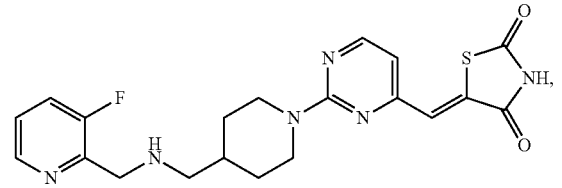

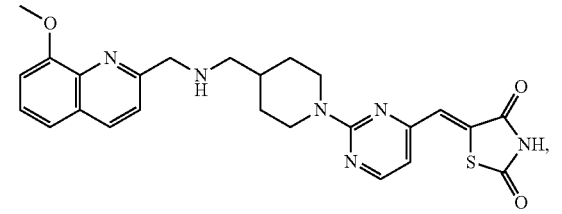

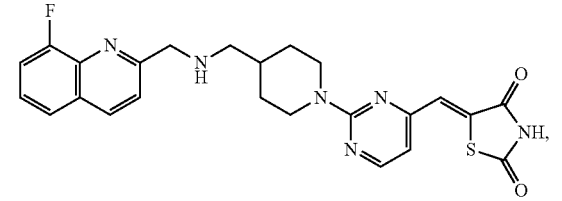

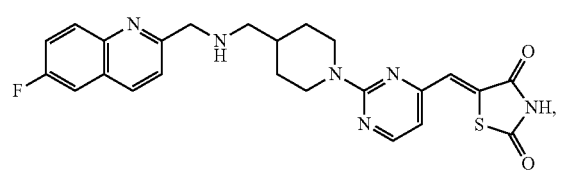

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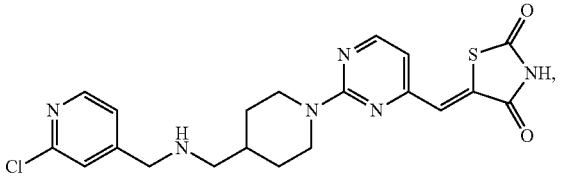

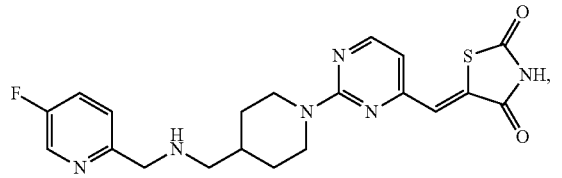

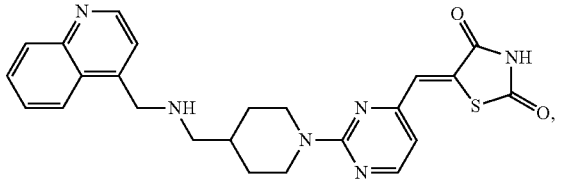

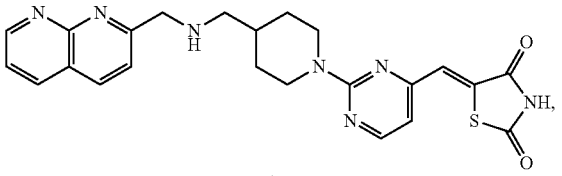

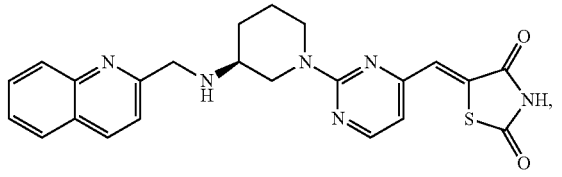

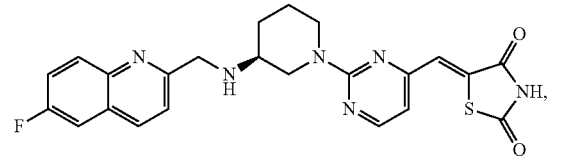

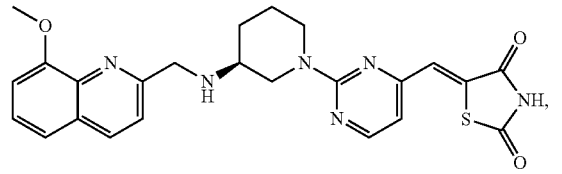

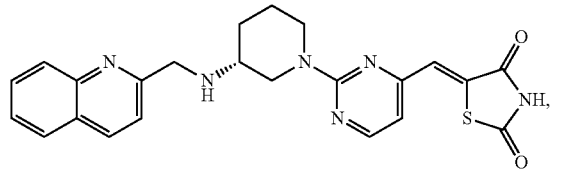

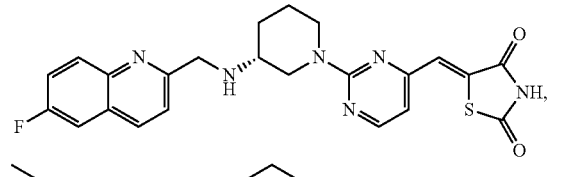

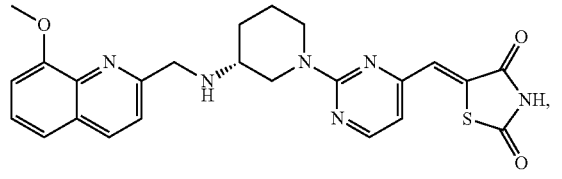

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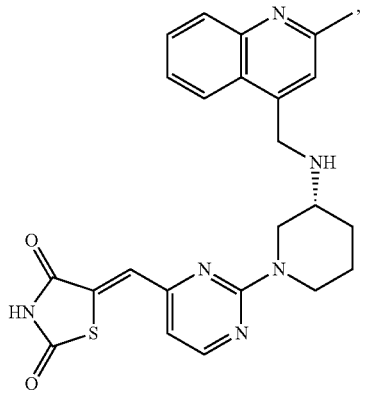

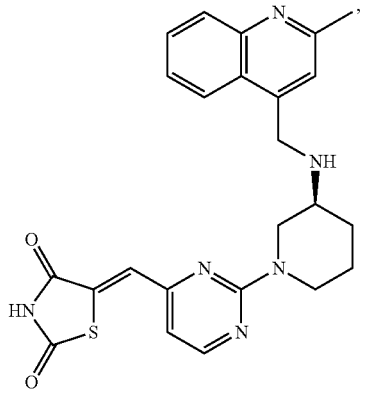

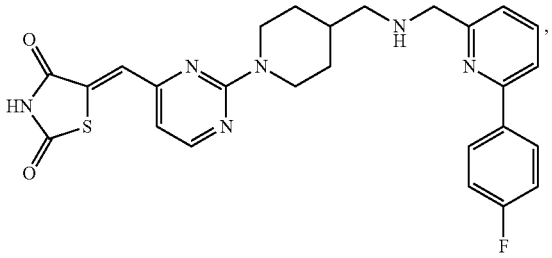

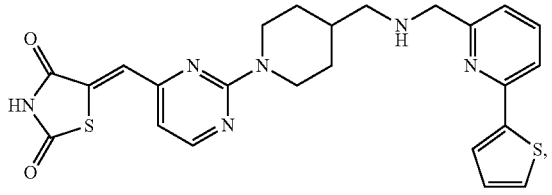

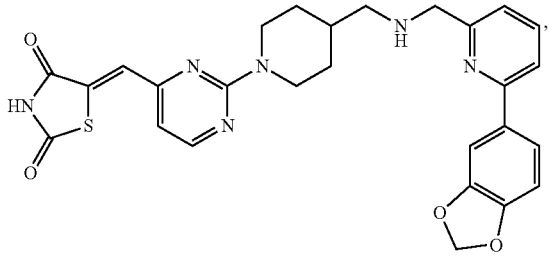

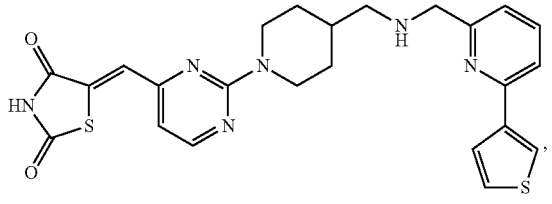

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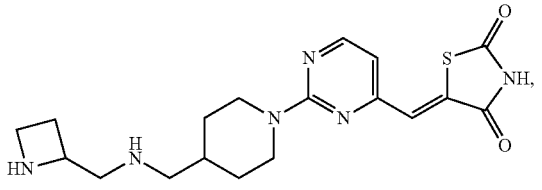

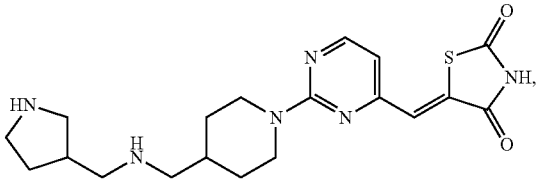

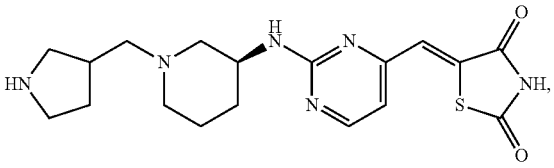

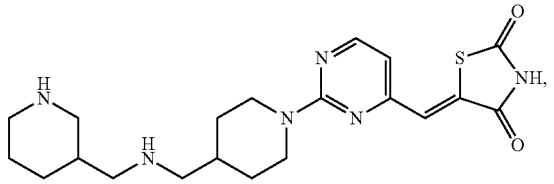

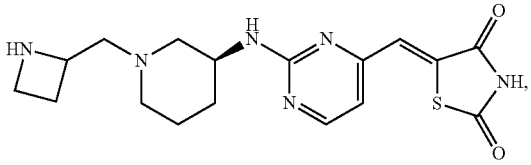

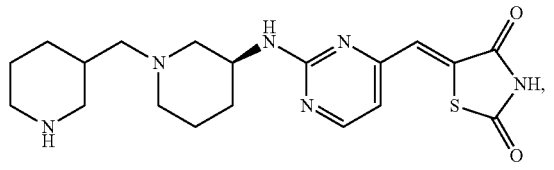

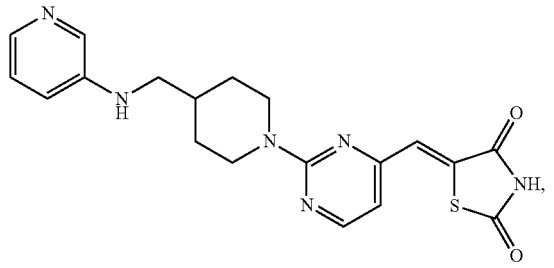

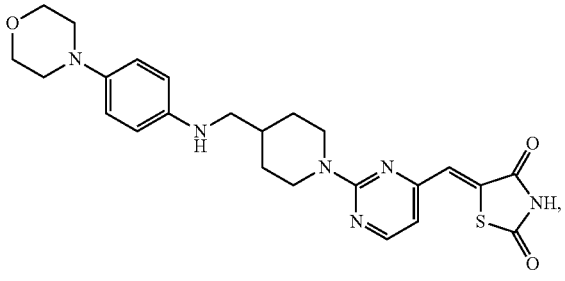

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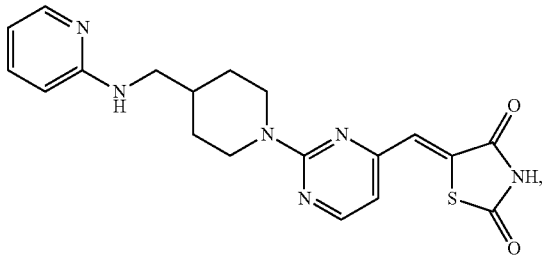

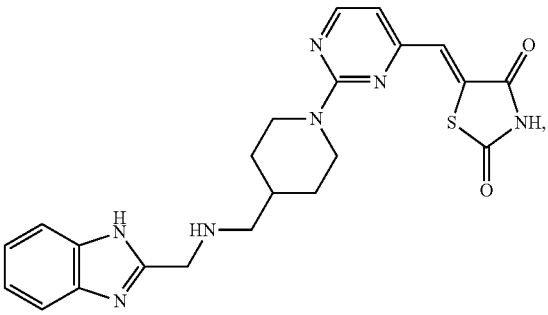

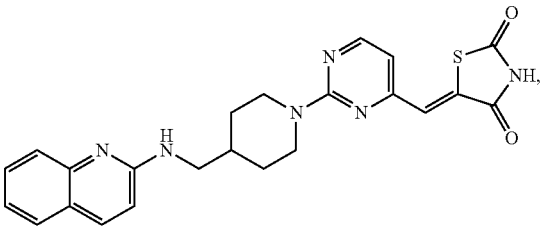

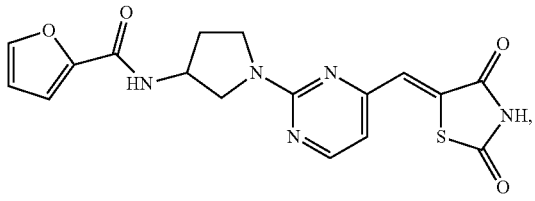

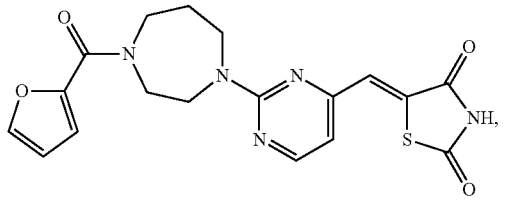

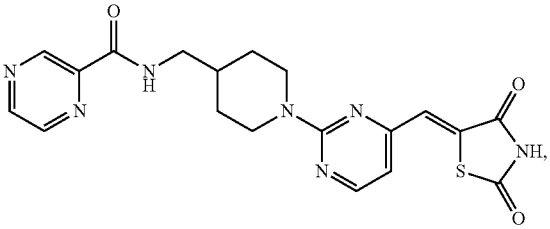

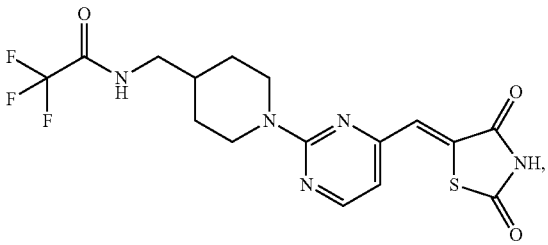

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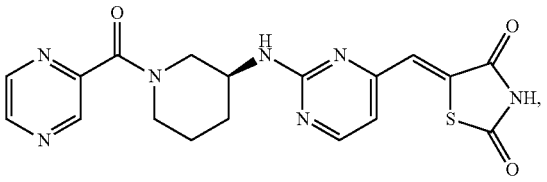

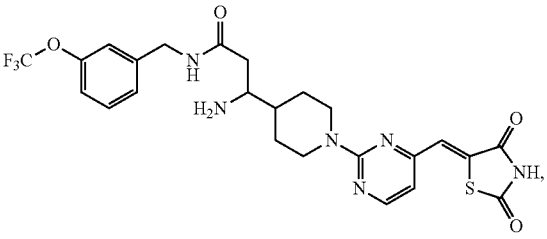

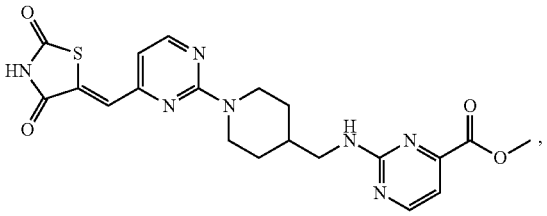

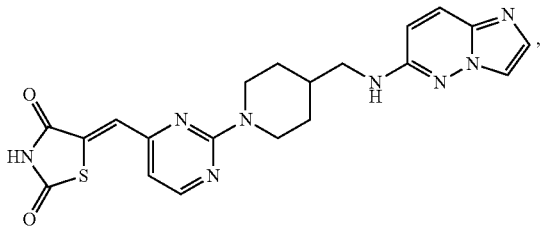

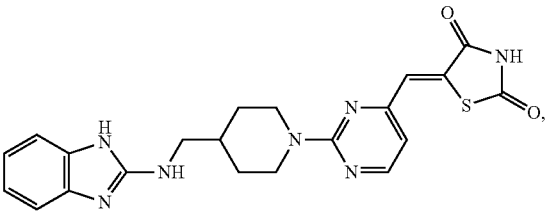

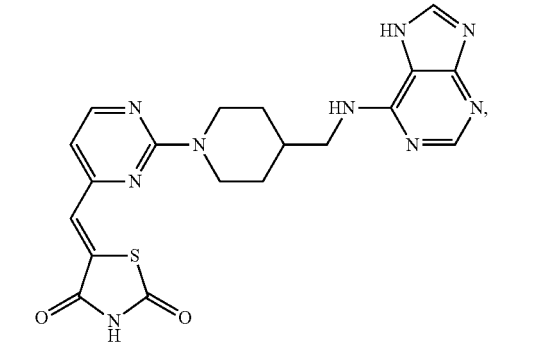

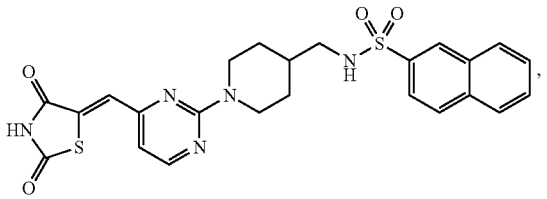

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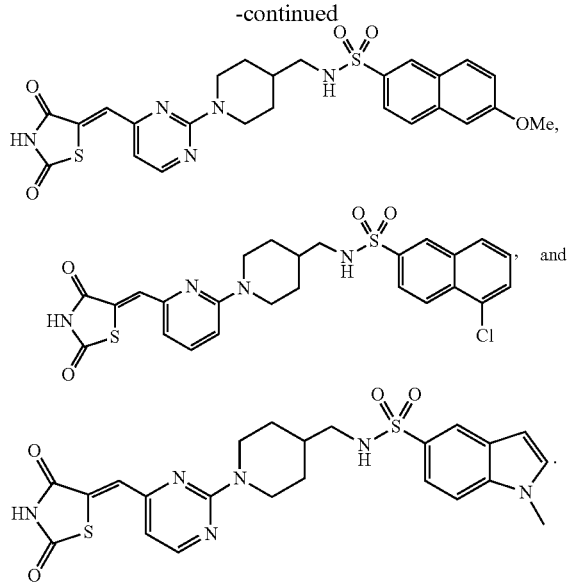


An embodiment relates to any one of the aforementioned compounds, wherein the compound is an inhibitor of CK1, CK1γ1, CK1γ2, or CK1γ3. In one embodiment the compound has an IC_{50} of less than 5000 nM for CK1, CK1γ1, CK1γ2, or CK1γ3. In one embodiment the compound has an IC_{50} of less than 1000 nM for CK1, CK1γ1, CK1γ2, or CK1γ3. In one embodiment the compound has an IC_{50} of less than 500 nM for CK1, CK1γ1, CK1γ2, or CK1γ3.

An embodiment relates to any one of the aforementioned compounds, wherein the compound is an inhibitor of CK2. In one embodiment the compound has an IC_{50} of less than 5000 nM for CK2. In one embodiment the compound has an IC_{50} of less than 1000 nM for CK2. In one embodiment the compound has an IC_{50} of less than 500 nM for CK2.

An embodiment relates to any one of the aforementioned compounds, wherein the compound is an inhibitor of PIM1, PIM2, or PIM3. In one embodiment the compound has an IC_{50} of less than 5000 nM for PIM1, PIM2, or PIM3. In one embodiment the compound has an IC_{50} of less than 1000 nM for PIM1, PIM2, or PIM3. In one embodiment the compound has an IC_{50} of less than 500 nM for PIM1, PIM2, or PIM3.

An embodiment relates to any one of the aforementioned compounds, wherein the compound is an inhibitor of the Wnt pathway.

An embodiment relates to any one of the aforementioned compounds, wherein the compound is an inhibitor of the TGFβ pathway.

An embodiment relates to any one of the aforementioned compounds, wherein the compound is an inhibitor of the JAK/STAT pathway.

An embodiment relates to any one of the aforementioned compounds, wherein the compound is an inhibitor of the mTOR pathway.

An embodiment relates to any one of the aforementioned compounds, wherein the compound is a modulator of Pgp degradation, drug efflux, or drug resistance.

An embodiment relates to a pharmaceutical composition comprising any one or combination of the aforementioned compounds, and a pharmaceutically acceptable carrier.

Another embodiment relates to a method of inhibiting CK1 activity, comprising contacting CK1, CK1γ1, CK1γ2, or CK1γ3 with any one of the aforementioned compounds or pharmaceutical compositions.

Another embodiment relates to a method of inhibiting CK2 activity, comprising contacting CK2 with any one of the aforementioned compounds or pharmaceutical compositions.

Another embodiment relates to a method of treating or preventing a condition associated with aberrant CK1, CK1γ1, CK1γ2, or CK1γ3 activity, comprising administering to a mammal in need thereof a therapeutically effective amount of any one of the aforementioned compounds or pharmaceutical compositions.

Another embodiment relates to a method of treating or preventing a condition associated with aberrant CK2 activity, comprising administering to a mammal in need thereof a therapeutically effective amount of any one of the aforementioned compounds or pharmaceutical compositions.

Another embodiment relates to a method of treating cancer, comprising administering to a mammal in need thereof a therapeutically effective amount of any one of the aforementioned compounds or pharmaceutical compositions. In one embodiment the cancer is a cancer of a system selected from the group consisting of the hematopoietic system, immune system, endocrine system, pulmonary system, gastrointestinal system, musculoskeletal system, reproductive system, central nervous system, and urologic system. In one embodiment the cancer is located in the mammal's myeloid tissues, lymphoid tissues, pancreatic tissues, thyroid tissues, lung tissues, colon tissues, rectal tissues, anal tissues, liver tissues, skin, bone, ovarian tissues, uterine tissues, cervical tissues, breast, prostate, testicular tissues, brain, brainstem, meningeal tissues, kidney or bladder. In one embodiment the cancer is selected from the group consisting of breast cancer, colon cancer, multiple myeloma, prostate cancer, Hodgkin's lymphoma, non-Hodgkin's lymphoma, leukemia, hematologic malignancy, renal cell carcinoma, renal cancer, malignant melanoma, pancreatic cancer, lung cancer, colorectal carcinoma, brain cancer, head and neck cancer, bladder cancer, thyroid cancer, ovarian cancer, cervical cancer, and myelodysplastic syndrome.

Another embodiment relates to a method of treating leukemia or other hematologic malignancies, comprising administering to a mammal in need thereof a therapeutically effective amount of any one of the aforementioned compounds or pharmaceutical compositions.

Another embodiment relates to a method of treating Alzheimer's disease, comprising administering to a mammal in need thereof a therapeutically effective amount of any one of the aforementioned compounds or pharmaceutical compositions.

Another embodiment relates to a method of treating a Wnt-dependent disease, comprising administering to a mammal in need thereof a therapeutically effective amount of any one of the aforementioned compounds or pharmaceutical compositions.

Another embodiment relates to a method of treating a TGFβ-dependent disease, comprising administering to a mammal in need thereof a therapeutically effective amount of any one of the aforementioned compounds or pharmaceutical compositions.

Another embodiment relates to a method of treating a JAK/STAT-dependent disease, comprising administering to a mammal in need thereof a therapeutically effective amount of any one of the aforementioned compounds or pharmaceutical compositions.

Another embodiment relates to a method of treating an mTOR-dependent disease, comprising administering to a

mammal in need thereof a therapeutically effective amount of any one of the aforementioned compounds or pharmaceutical compositions.

Another embodiment relates to a method of treating or preventing inflammation, inflammatory diseases (e.g., osteoarthritis and rheumatoid arthritis), neurological conditions (e.g., Alzheimer's disease) and neurodegeneration, comprising administering to a mammal in need thereof a therapeutically effective amount of any one of the aforementioned compounds or pharmaceutical compositions.

Another embodiment relates to a method of treating or preventing bone-related diseases and conditions, including osteoporosis and bone formation, or facilitating bone restoration, comprising administering to a mammal in need thereof a therapeutically effective amount of any one of the aforementioned compounds or pharmaceutical compositions.

Another embodiment relates to a method of treating or preventing hypoglycemia, metabolic syndrome and diabetes, comprising administering to a mammal in need thereof a therapeutically effective amount of any one of the aforementioned compounds or pharmaceutical compositions.

Another embodiment relates to a method of influencing apoptosis (e.g., increasing the rate of apoptosis in cancerous cells), comprising administering to a mammal in need thereof a therapeutically effective amount of any one of the aforementioned compounds or pharmaceutical compositions.

Another embodiment relates to a method of treating or preventing aberrant embryonic development, comprising administering to a mammal in need thereof a therapeutically effective amount of any one of the aforementioned compounds or pharmaceutical compositions.

Another embodiment relates to a method of inhibiting PIM activity, comprising contacting PIM1, PIM2 or PIM3 with any one of the aforementioned compounds or pharmaceutical compositions.

Another embodiment relates to a method for treating or preventing a condition associated with aberrant PIM activity, comprising administering to a mammal in need thereof a therapeutically effective amount of any one of the aforementioned compounds or pharmaceutical compositions.

Another embodiment relates to a method of modulating Pgp degradation and/or drug efflux activity, comprising contacting a cell with any one of the aforementioned compounds or pharmaceutical compositions.

Another embodiment relates to a method for treating a malignancy based upon modulation of Pgp, comprising administering to a mammal in need thereof a therapeutically effective amount of any one of the aforementioned compounds or pharmaceutical compositions.

Another embodiment relates to a method for treating a malignancy based upon modulation of Pgp, comprising administering to a mammal in need thereof a therapeutically effective amount of any one of the aforementioned compounds or pharmaceutical compositions, in conjunction with another drug, compound, or material, to abrogate resistance to the drug, compound, or material.

BRIEF DESCRIPTION OF THE FIGURES

FIG. **1** depicts the relative activity of CK1γ1(h) as a function of the concentration of compound 4981.

FIG. **2** depicts the relative activity of CK1γ2(h) as a function of the concentration of compound 4981.

FIG. **3** depicts the relative activity of CK1γ3(h) as a function of the concentration of compound 4981.

FIG. **4** depicts the relative activity of CK1δ(h) as a function of the concentration of compound 4981.

FIG. **5** depicts the relative activity of CK1(y) as a function of the concentration of compound 4981.

FIG. **6** depicts the relative activity of CK1γ1(h) as a function of the concentration of compound 4993.

FIG. **7** depicts the relative activity of CK1γ2(h) as a function of the concentration of compound 4993.

FIG. **8** depicts the relative activity of CK1γ3(h) as a function of the concentration of compound 4993.

FIG. **9** depicts the relative activity of CK1δ(h) as a function of the concentration of compound 4993.

FIG. **10** depicts the relative activity of CK1(y) as a function of the concentration of compound 4993.

FIG. **11** depicts the relative activity of CK1γ1(h) as a function of the concentration of compound 4991.

FIG. **12** depicts the relative activity of CK1γ2(h) as a function of the concentration of compound 4991.

FIG. **13** depicts the relative activity of CK1γ3(h) as a function of the concentration of compound 4991.

FIG. **14** depicts the relative activity of CK1δ(h) as a function of the concentration of compound 4991.

FIG. **15** depicts the relative activity of CK1(y) as a function of the concentration of compound 4991.

FIG. **16** depicts the relative activity of CK1γ1(h) as a function of the concentration of compound 4999.

FIG. **17** depicts the relative activity of CK1γ2(h) as a function of the concentration of compound 4999.

FIG. **18** depicts the relative activity of CK1γ3(h) as a function of the concentration of compound 4999.

FIG. **19** depicts the relative activity of CK1δ(h) as a function of the concentration of compound 4999.

FIG. **20** depicts the relative activity of CK1(y) as a function of the concentration of compound 4999.

FIG. **21** depicts the relative activity of CK1γ1(h) as a function of the concentration of compound 4985.

FIG. **22** depicts the relative activity of CK1γ2(h) as a function of the concentration of compound 4985.

FIG. **23** depicts the relative activity of CK1γ3(h) as a function of the concentration of compound 4985.

FIG. **24** depicts the relative activity of CK1δ(h) as a function of the concentration of compound 4985.

FIG. **25** depicts the relative activity of CK1(y) as a function of the concentration of compound 4985.

FIG. **26** depicts the relative activity of CK1γ1(h) as a function of the concentration of compound 4992.

FIG. **27** depicts the relative activity of CK1γ2(h) as a function of the concentration of compound 4992.

FIG. **28** depicts the relative activity of CK1γ3(h) as a function of the concentration of compound 4992.

FIG. **29** depicts the relative activity of CK1δ(h) as a function of the concentration of compound 4992.

FIG. **30** depicts the relative activity of CK1(y) as a function of the concentration of compound 4992.

FIG. **31** depicts the relative activity of CK1γ1(h) as a function of the concentration of compound 4996.

FIG. **32** depicts the relative activity of CK1γ2(h) as a function of the concentration of compound 4996.

FIG. **33** depicts the relative activity of CK1γ3(h) as a function of the concentration of compound 4996.

FIG. **34** depicts the relative activity of CK1δ(h) as a function of the concentration of compound 4996.

FIG. **35** depicts the relative activity of CK1(y) as a function of the concentration of compound 4996.

FIG. **36** depicts the relative activity of CK1γ1(h) as a function of the concentration of compound 5000.

FIG. **37** depicts the relative activity of CK1γ2(h) as a function of the concentration of compound 5000.

FIG. **38** depicts the relative activity of CK1γ3(h) as a function of the concentration of compound 5000.

FIG. **39** depicts the relative activity of CK1δ(h) as a function of the concentration of compound 5000.

FIG. **40** depicts the relative activity of CK1(y) as a function of the concentration of compound 5000.

FIG. **41** depicts the dose-response curve and EC_{50} of gemcitabine against PC-3 cells, which data served as an experimental control.

FIG. **42** depicts the dose-response curve and EC_{50} of gemcitabine against OVCAR-3 cells, which data served as an experimental control.

FIG. **43** depicts the dose-response curve and EC_{50} of gemcitabine against LNCaP cells, which data served as an experimental control.

FIG. **44** depicts the dose-response curve and EC_{50} of gemcitabine against Jurkat cells, which data served as an experimental control.

FIG. **45** depicts the dose-response curve and EC_{50} of gemcitabine against MDA-MB-468 cells, which data served as an experimental control.

FIG. **46** depicts the dose-response curve and IC_{50} of gemcitabine against HCT116 cells, which data served as an experimental control.

FIG. **47** depicts the dose-response curve and IC_{50} of gemcitabine against A549 cells, which data served as an experimental control.

FIG. **48** depicts the dose-response curve and IC_{50} of gemcitabine against DU145 cells, which data served as an experimental control.

FIG. **49** depicts the dose-response curve and IC_{50} of sorafenib against HC1954 cells, which data served as an experimental control.

FIG. **50** depicts the dose-response curve and EC_{50} of sorafenib against Caco-2 cells, which data served as an experimental control.

FIG. **51** depicts the dose response curve and IC_{50} of compound 4991 against OVCAR-3 cells compared to cisplatin.

FIG. **52** depicts the dose response curve and IC_{50} of compound 4991 against OVCAR-8 cells compared to cisplatin.

FIG. **53** depicts the dose response curve and IC_{50} of compound 4991 against SK-OV-3 cells compared to cisplatin.

DETAILED DESCRIPTION OF THE INVENTION

Definitions

The definitions of terms used herein are meant to incorporate the present state-of-the-art definitions recognized for each term in the chemical and pharmaceutical fields. Where appropriate, illustration is provided. The definitions apply to the terms as they are used throughout this specification, unless otherwise limited in specific instances, either individually or as part of a larger group.

Where stereochemistry is not specifically indicated, all stereoisomers of the inventive compounds are included within the scope of the invention, as pure compounds as well as mixtures thereof. Unless otherwise indicated, individual enantiomers, diastereomers, geometrical isomers, and combinations and mixtures thereof are all encompassed by the present invention. Polymorphic crystalline forms and solvates are also encompassed within the scope of this invention.

As used herein, the term "isolated" in connection with a compound of the present invention means the compound is not in a cell or organism and the compound is separated from some or all of the components that typically accompany it in nature.

As used herein, the term "pure" in connection with an isolated sample of a compound of the present invention means the isolated sample contains at least 60% by weight of the compound. Preferably, the isolated sample contains at least 70% by weight of the compound. More preferably, the isolated sample contains at least 80% by weight of the compound. Even more preferably, the isolated sample contains at least 90% by weight of the compound. Most preferably, the isolated sample contains at least 95% by weight of the compound. The purity of an isolated sample of a compound of the present invention may be assessed by a number of methods or a combination of them; e.g., thin-layer, preparative or flash chromatography, mass spectrometry, HPLC, NMR analysis, and the like.

The term "heteroatom" is art-recognized and refers to an atom of any element other than carbon or hydrogen. Illustrative heteroatoms include boron, nitrogen, oxygen, phosphorus, sulfur and selenium.

The term "alkyl" is art-recognized, and includes saturated aliphatic groups, including straight-chain alkyl groups, branched-chain alkyl groups, cycloalkyl (alicyclic) groups, alkyl substituted cycloalkyl groups, and cycloalkyl substituted alkyl groups. In certain embodiments, a straight chain or branched chain alkyl has about 30 or fewer carbon atoms in its backbone (e.g., C_1-C_{30} for straight chain, C_3-C_{30} for branched chain), and alternatively, about 20 or fewer. Likewise, cycloalkyls have from about 3 to about 10 carbon atoms in their ring structure, and alternatively about 5, 6 or 7 carbons in the ring structure.

Unless the number of carbons is otherwise specified, "lower alkyl" refers to an alkyl group, as defined above, but having from one to about ten carbons, alternatively from one to about six carbon atoms in its backbone structure. Likewise, "lower alkenyl" and "lower alkynyl" have similar chain lengths.

The term "aralkyl" is art-recognized and refers to an alkyl group substituted with an aryl group (e.g., an aromatic or heteroaromatic group).

The terms "alkenyl" and "alkynyl" are art-recognized and refer to unsaturated aliphatic groups analogous in length and possible substitution to the alkyls described above, but that contain at least one double or triple bond respectively.

The term "aryl" is art-recognized and refers to 5-, 6- and 7-membered single-ring aromatic groups that may include from zero to four heteroatoms, for example, benzene, naphthalene, anthracene, pyrene, pyrrole, furan, thiophene, imidazole, oxazole, thiazole, triazole, pyrazole, pyridine, pyrazine, pyridazine and pyrimidine, and the like. Those aryl groups having heteroatoms in the ring structure may also be referred to as "aryl heterocycles" or "heteroaromatics." The aromatic ring may be substituted at one or more ring positions with such substituents as described above, for example, halogen, azide, alkyl, aralkyl, alkenyl, alkynyl, cycloalkyl, hydroxyl, alkoxyl, amino, nitro, sulfhydryl, imino, amido, phosphonate, phosphinate, carbonyl, carboxyl, silyl, ether, alkylthio, sulfonyl, sulfonamido, ketone, aldehyde, ester, heterocyclyl, aromatic or heteroaromatic moieties, —CF_3, —CN, or the like. The term "aryl" also includes polycyclic ring systems having two or more cyclic rings in which two or more carbons are common to two adjoining rings (the rings are "fused rings") wherein at least one of the rings is aromatic, e.g., the other cyclic rings may be cycloalkyls, cycloalkenyls, cycloalkynyls, aryls and/or heterocyclyls.

The terms ortho, meta and para are art-recognized and refer to 1,2-, 1,3- and 1,4-disubstituted benzenes, respectively. For example, the names 1,2-dimethylbenzene and ortho-dimethylbenzene are synonymous.

The terms "heterocyclyl", "heteroaryl", or "heterocyclic group" are art-recognized and refer to 3- to about 10-membered ring structures, alternatively 3- to about 7-membered rings, whose ring structures include one to four heteroatoms. Heterocycles may also be polycycles. Heterocyclyl groups include, for example, thiophene, thianthrene, furan, pyran, isobenzofuran, chromene, xanthene, phenoxanthene, pyrrole, imidazole, pyrazole, isothiazole, isoxazole, pyridine, pyrazine, pyrimidine, pyridazine, indolizine, isoindole, indole, indazole, purine, quinolizine, isoquinoline, quinoline, phthalazine, naphthyridine, quinoxaline, quinazoline, cinnoline, pteridine, carbazole, carboline, phenanthridine, acridine, pyrimidine, phenanthroline, phenazine, phenarsazine, phenothiazine, piperonyl, furazan, phenoxazine, pyrrolidine, oxolane, thiolane, oxazole, piperidine, piperazine, morpholine, lactones, lactams such as azetidinones and pyrrolidinones, sultams, sultones, and the like. The heterocyclic ring may be substituted at one or more positions with such substituents as described above, as for example, halogen, alkyl, aralkyl, alkenyl, alkynyl, cycloalkyl, hydroxyl, amino, nitro, sulfhydryl, imino, amido, phosphonate, phosphinate, carbonyl, carboxyl, silyl, ether, alkylthio, sulfonyl, ketone, aldehyde, ester, a heterocyclyl, an aromatic or heteroaromatic moiety, —CF_3, —CN, or the like.

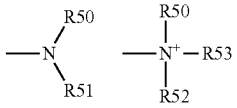
The term "optionally substituted" refers to a chemical group, such as alkyl, cycloalkyl aryl, and the like, wherein one or more hydrogen may be replaced with a substituent as described herein, including but not limited to halogen, azide, alkyl, aralkyl, alkenyl, alkynyl, cycloalkyl, hydroxyl, alkoxyl, amino, nitro, sulfhydryl, imino, amido, phosphonate, phosphinate, carbonyl, carboxyl, silyl, ether, alkylthio, sulfonyl, sulfonamido, ketone, aldehyde, ester, heterocyclyl, aromatic or heteroaromatic moieties, —CF_3, —CN, or the like.

The terms "polycyclyl" or "polycyclic group" are art-recognized and refer to two or more rings (e.g., cycloalkyls, cycloalkenyls, cycloalkynyls, aryls and/or heterocyclyls) in which two or more carbons are common to two adjoining rings, e.g., the rings are "fused rings". Rings that are joined through non-adjacent atoms are termed "bridged" rings. Each of the rings of the polycycle may be substituted with such substituents as described above, as for example, halogen, alkyl, aralkyl, alkenyl, alkynyl, cycloalkyl, hydroxyl, amino, nitro, sulfhydryl, imino, amido, phosphonate, phosphinate, carbonyl, carboxyl, silyl, ether, alkylthio, sulfonyl, ketone, aldehyde, ester, a heterocyclyl, an aromatic or heteroaromatic moiety, —CF_3, —CN, or the like.

The term "carbocycle" is art-recognized and refers to an aromatic or non-aromatic ring in which each atom of the ring is carbon.

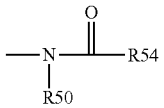
The term "nitro" is art-recognized and refers to —NO_2; the term "halogen" is art-recognized and refers to —F, —Cl, —Br or —I; the term "sulfhydryl" is art-recognized and refers to —SH; the term "hydroxyl" means —OH; and the term "sulfonyl" is art-recognized and refers to —SO_2^-. "Halide" designates the corresponding anion of the halogens, and "pseudohalide" has the definition set forth on 560 of *Advanced Inorganic Chemistry* by Cotton and Wilkinson.

The terms "amine" and "amino" are art-recognized and refer to both unsubstituted and substituted amines, e.g., a moiety that may be represented by the general formulas:



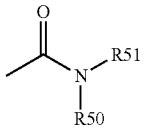
wherein R50, R51 and R52 each independently represent a hydrogen, an alkyl, an alkenyl, —$(CH_2)_m$—R61, or R50 and R51, taken together with the N atom to which they are attached complete a heterocycle having from 4 to 8 atoms in the ring structure; R61 represents an aryl, a cycloalkyl, a cycloalkenyl, a heterocycle or a polycycle; and m is zero or an integer in the range of 1 to 8. In other embodiments, R50 and R51 (and optionally R52) each independently represent a hydrogen, an alkyl, an alkenyl, or —$(CH_2)_m$—R61. Thus, the term "alkylamine" includes an amine group, as defined above, having a substituted or unsubstituted alkyl attached thereto, i.e., at least one of R50 and R51 is an alkyl group.

The term "acylamino" is art-recognized and refers to a moiety that may be represented by the general formula:



wherein R50 is as defined above, and R54 represents a hydrogen, an alkyl, an alkenyl or —$(CH_2)_m$—R61, where m and R61 are as defined above.

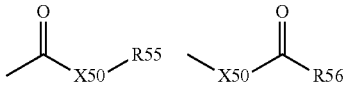
The term "amido" is art recognized as an amino-substituted carbonyl and includes a moiety that may be represented by the general formula:



wherein R50 and R51 are as defined above. Certain embodiments of the amide in the present invention will not include imides which may be unstable.

The term "alkylthio" refers to an alkyl group, as defined above, having a sulfur radical attached thereto. In certain embodiments, the "alkylthio" moiety is represented by one of —S-alkyl, —S-alkenyl, —S-alkynyl, and —S—$(CH_2)_m$—R61, wherein m and R61 are defined above. Representative alkylthio groups include methylthio, ethyl thio, and the like.

The term "carboxyl" is art recognized and includes such moieties as may be represented by the general formulas:



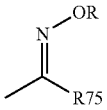
wherein X50 is a bond or represents an oxygen or a sulfur, and R55 and R56 represents a hydrogen, an alkyl, an alkenyl, —$(CH_2)_m$—R61 or a pharmaceutically acceptable salt, R56 represents a hydrogen, an alkyl, an alkenyl or —$(CH_2)_m$—R61, where m and R61 are defined above. Where X50 is an oxygen and R55 or R56 is not hydrogen, the formula represents an "ester". Where X50 is an oxygen, and R55 is as

defined above, the moiety is referred to herein as a carboxyl group, and particularly when R55 is a hydrogen, the formula represents a "carboxylic acid". Where X50 is an oxygen, and R56 is hydrogen, the formula represents a "formate". In general, where the oxygen atom of the above formula is replaced by sulfur, the formula represents a "thiolcarbonyl" group. Where X50 is a sulfur and R55 or R56 is not hydrogen, the formula represents a "thiolester." Where X50 is a sulfur and R55 is hydrogen, the formula represents a "thiolcarboxylic acid." Where X50 is a sulfur and R56 is hydrogen, the formula represents a "thiolformate." On the other hand, where X50 is a bond, and R55 is not hydrogen, the above formula represents a "ketone" group. Where X50 is a bond, and R55 is hydrogen, the above formula represents an "aldehyde" group.

The term "carbamoyl" refers to —O(C═O)NRR', where R and R' are independently H, aliphatic groups, aryl groups or heteroaryl groups.

The term "oxo" refers to a carbonyl oxygen (═O).

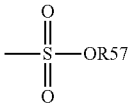
The terms "oxime" and "oxime ether" are art-recognized and refer to moieties that may be represented by the general formula:



wherein R75 is hydrogen, alkyl, cycloalkyl, alkenyl, alkynyl, aryl, aralkyl, or $—(CH_2)_m—R61$. The moiety is an "oxime" when R is H; and it is an "oxime ether" when R is alkyl, cycloalkyl, alkenyl, alkynyl, aryl, aralkyl, or $—(CH_2)_m—R61$.

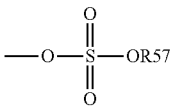
The terms "alkoxyl" or "alkoxy" are art-recognized and refer to an alkyl group, as defined above, having an oxygen radical attached thereto. Representative alkoxyl groups include methoxy, ethoxy, propyloxy, tert-butoxy and the like. An "ether" is two hydrocarbons covalently linked by an oxygen. Accordingly, the substituent of an alkyl that renders that alkyl an ether is or resembles an alkoxyl, such as may be represented by one of —O-alkyl, —O-alkenyl, —O-alkynyl, $—O—(CH_2)_m—R61$, where m and R61 are described above.

The term "sulfonate" is art recognized and refers to a moiety that may be represented by the general formula:



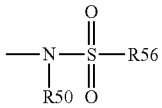
in which R57 is an electron pair, hydrogen, alkyl, cycloalkyl, or aryl.

The term "sulfate" is art recognized and includes a moiety that may be represented by the general formula:



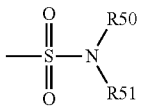
in which R57 is as defined above.

The term "sulfonamido" is art recognized and includes a moiety that may be represented by the general formula:



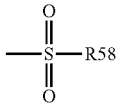
in which R50 and R56 are as defined above.

The term "sulfamoyl" is art-recognized and refers to a moiety that may be represented by the general formula:



in which R50 and R51 are as defined above.

The term "sulfonyl" is art-recognized and refers to a moiety that may be represented by the general formula:

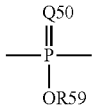


in which R58 is one of the following: hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl or heteroaryl.

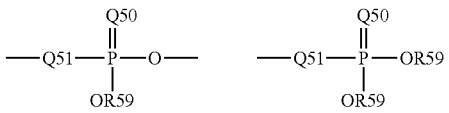
The term "sulfoxido" is art-recognized and refers to a moiety that may be represented by the general formula:

in which R58 is defined above.

The term "phosphoryl" is art-recognized and may in general be represented by the formula:

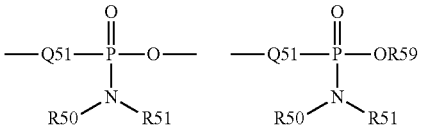


wherein Q50 represents S or O, and R59 represents hydrogen, a lower alkyl or an aryl. When used to substitute, e.g., an alkyl, the phosphoryl group of the phosphorylalkyl may be represented by the general formulas:



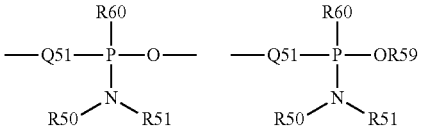
wherein Q50 and R59, each independently, are defined above, and Q51 represents O, S or N. When Q50 is S, the phosphoryl moiety is a "phosphorothioate".

The term "phosphoramidite" is art-recognized and may be represented in the general formulas:



wherein Q51, R50, R51 and R59 are as defined above.

The term "phosphonamidite" is art-recognized and may be represented in the general formulas:



wherein Q51, R50, R51 and R59 are as defined above, and R60 represents a lower alkyl or an aryl.

Analogous substitutions may be made to alkenyl and alkynyl groups to produce, for example, aminoalkenyls, aminoalkynyls, amidoalkenyls, amidoalkynyls, iminoalkenyls, iminoalkynyls, thioalkenyls, thioalkynyls, carbonyl-substituted alkenyls or alkynyls.

The definition of each expression, e.g., alkyl, m, n, and the like, when it occurs more than once in any structure, is intended to be independent of its definition elsewhere in the same structure.

The terms triflyl, tosyl, mesyl, and nonaflyl are art-recognized and refer to trifluoromethanesulfonyl, p-toluenesulfonyl, methanesulfonyl, and nonafluorobutanesulfonyl groups, respectively. The terms triflate, tosylate, mesylate, and nonaflate are art-recognized and refer to trifluoromethanesulfonate ester, p-toluenesulfonate ester, methanesulfonate ester, and nonafluorobutanesulfonate ester functional groups and molecules that contain said groups, respectively.

The abbreviations Me, Et, Ph, Tf, Nf, Ts, and Ms represent methyl, ethyl, phenyl, trifluoromethanesulfonyl, nonafluorobutanesulfonyl, p-toluenesulfonyl and methanesulfonyl, respectively. A more comprehensive list of the abbreviations utilized by organic chemists of ordinary skill in the art appears in the first issue of each volume of the *Journal of Organic Chemistry*; this list is typically presented in a table entitled "Standard List of Abbreviations."

Certain compounds contained in compositions of the present invention may exist in particular geometric or stereoisomeric forms. In addition, polymers of the present invention may also be optically active. The present invention contemplates all such compounds, including cis- and trans-isomers, E- and Z-isomers, R- and S-enantiomers, diastereomers, (D)-isomers, (L)-isomers, the racemic mixtures thereof, and other mixtures thereof, as falling within the scope of the invention. Additional asymmetric carbon atoms may be present in a substituent such as an alkyl group. All such isomers, as well as mixtures thereof, are intended to be included in this invention.

If, for instance, a particular enantiomer of compound of the present invention is desired, it may be prepared by asymmetric synthesis, or by derivation with a chiral auxiliary, where the resulting diastereomeric mixture is separated and the auxiliary group cleaved to provide the pure desired enantiomers. Alternatively, where the molecule contains a basic functional group, such as amino, or an acidic functional group, such as carboxyl, diastereomeric salts are formed with an appropriate optically-active acid or base, followed by resolution of the diastereomers thus formed by fractional crystallization or chromatographic means well known in the art, and subsequent recovery of the pure enantiomers.

It will be understood that "substitution" or "substituted with" includes the implicit proviso that such substitution is in accordance with permitted valence of the substituted atom and the substituent, and that the substitution results in a stable compound, e.g., which does not spontaneously undergo transformation such as by rearrangement, cyclization, elimination, or other reaction.

The term "substituted" is also contemplated to include all permissible substituents of organic compounds. In a broad aspect, the permissible substituents include acyclic and cyclic, branched and unbranched, carbocyclic and heterocyclic, aromatic and nonaromatic substituents of organic compounds. Illustrative substituents include, for example, those described herein above. The permissible substituents may be one or more and the same or different for appropriate organic compounds. For purposes of this invention, the heteroatoms such as nitrogen may have hydrogen substituents and/or any permissible substituents of organic compounds described herein which satisfy the valences of the heteroatoms. This invention is not intended to be limited in any manner by the permissible substituents of organic compounds.

The phrase "protecting group" as used herein means temporary substituents which protect a potentially reactive functional group from undesired chemical transformations. Examples of such protecting groups include esters of carboxylic acids, silyl ethers of alcohols, and acetals and ketals of aldehydes and ketones, respectively. Examples of nitrogen protecting groups include an amide (—NRC(=O)R) or a urethane (—NRC(=O)OR), for example, as: a methyl amide (—NHC(=O)CH_3); a benzyloxy amide (—NHC(=O)$OCH_2C_6H_5$NHCbz); as a t-butoxy amide (—NHC(=O)O$C(CH_3)_3$, —NHBoc); a 2-biphenyl-2-propoxy amide (—NHC(=O)O$C(CH_3)_2C_6H_4C_6H_5$NHBoc), as a 9-fluorenylmethoxy amide (—NHFmoc), as a 6-nitroveratryloxy amide (—NHNvoc), as a 2-trimethylsilylethyloxy amide (—NHTeoc), as a 2,2,2-trichloroethyloxy amide (—NHTroc), as an allyloxy amide (—NHAlloc), as a 2-(phenylsulfonyl)ethyloxy amide (—NHPsec); or, in suitable cases (e.g., cyclic amines), as a nitroxide radical. The field of protecting group chemistry has been reviewed (Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis,* 2nd ed.; Wiley: New York, 1991). Protected forms of the inventive compounds are included within the scope of this invention.

The term "pharmaceutically acceptable salt" or "salt" refers to a salt of one or more compounds. Suitable pharmaceutically acceptable salts of compounds include acid addition salts, such as those formed with mineral acids such as hydrochloric acid and hydrobromic acid, and also those formed with organic acids such as maleic acid. For example, acids commonly employed to form pharmaceutically acceptable salts include inorganic acids such as hydrogen bisulfide, hydrochloric, hydrobromic, hydroiodic, sulfuric and phosphoric acid, as well as organic acids such as para-toluenesulfonic, salicylic, tartaric, bitartaric, ascorbic, maleic, besylic, fumaric, gluconic, glucuronic, formic, glutamic, methanesulfonic, ethanesulfonic, benzenesulfonic, lactic, oxalic, para-bromophenylsulfonic, carbonic, succinic, citric, benzoic and acetic acid, and related inorganic and organic acids. Such pharmaceutically acceptable salts thus include sulfate, pyrosulfate, bisulfate, sulfite, bisulfite, phosphate, monohydrogenphosphate, dihydrogenphosphate, metaphos-

phate, pyrophosphate, chloride, bromide, iodide, acetate, propionate, decanoate, caprylate, acrylate, formate, isobutyrate, caprate, heptanoate, propiolate, oxalate, malonate, succinate, suberate, sebacate, fumarate, maleate, butyne-1,4-dioate, hexyne-1,6-dioate, benzoate, chlorobenzoate, methylbenzoate, dinitrobenzoate, hydroxybenzoate, methoxybenzoate, phthalate, terephathalate, sulfonate, xylenesulfonate, phenylacetate, phenylpropionate, phenylbutyrate, citrate, lactate, β-hydroxybutyrate, glycolate, maleate, tartrate, methanesulfonate, propanesulfonate, naphthalene-1-sulfonate, naphthalene-2-sulfonate, mandelate and the like.

Where the compounds carry one or more acidic moieties, pharmaceutically acceptable salts may be formed by treatment of a solution of the compound with a solution of a pharmaceutically acceptable base. Suitable bases for forming pharmaceutically acceptable salts with acidic functional groups include, but are not limited to, hydroxides and carbonates of alkali metals such as sodium, potassium, and lithium; alkaline earth metal such as calcium and magnesium; and other metals, such as aluminum and zinc. Suitable bases also include ammonia, and organic amines, such as unsubstituted or hydroxy-substituted mono-, di-, or trialkylamines; dicyclohexylamine; tributyl amine; pyridine; N-methyl,N-ethylamine; diethylamine; triethylamine; mono-, bis-, or tris-(2-hydroxy-lower alkyl amines), such as mono-, bis-, or tris-(2-hydroxyethyl)amine, 2-hydroxy-tert-butylamine, or tris-(hydroxymethyl)methylamine, N,N-di alkyl-N-(hydroxy alkyl)-amines, such as N,N-dimethyl-N-(2-hydroxyethyl) amine, or tri-(2-hydroxyethyl)amine; N-methyl-D-glucamine; and amino acids such as arginine, lysine, and the like.

Certain compounds of the invention and their salts may exist in more than one crystalline form (i.e., polymorph); the present invention includes each of the crystal forms and mixtures thereof.

Certain compounds of the invention and their salts may also exist in the form of solvates, for example hydrates, and the present invention includes each solvate and mixtures thereof.

Certain compounds of the invention may contain one or more chiral centers, and exist in different optically active forms. When compounds of the invention contain one chiral center, the compounds exist in two enantiomeric forms and the present invention includes both enantiomers and mixtures of enantiomers, such as racemic mixtures thereof. The enantiomers may be resolved by methods known to those skilled in the art; for example, enantiomers may be resolved by formation of diastereoisomeric salts which may be separated, for example, by crystallization; formation of diastereoisomeric derivatives or complexes which may be separated, for example, by crystallization, gas-liquid or liquid chromatography; selective reaction of one enantiomer with an enantiomer-specific reagent, for example, via enzymatic esterification; or gas-liquid or liquid chromatography in a chiral environment, for example, on a chiral support; suitable include chiral supports (e.g., silica with a bound chiral ligand) or in the presence of a chiral solvent. Where the desired enantiomer is converted into another chemical entity by one of the separation procedures described above, a further step may be used to liberate the desired purified enantiomer. Alternatively, specific enantiomers may be synthesized by asymmetric synthesis using optically active reagents, substrates, catalysts or solvents, or by converting one enantiomer into the other by asymmetric transformation.

When a compound of the invention contains more than one chiral center, it may exist in diastereoisomeric forms. The diastereoisomeric compounds may be separated by methods known to those skilled in the art (for example, chromatography or crystallization) and the individual enantiomers may be separated as described above. The present invention includes the various diastereoisomers of compounds of the invention, and mixtures thereof. Compounds of the invention may exist in different tautomeric forms or as different geometric isomers, and the present invention includes each tautomer and/or geometric isomer of compounds of the invention, and mixtures thereof. For example, any olefins present in the compounds may exist as either the E- or Z-geometric isomers or a mixture thereof unless stated otherwise. Compounds of the invention may exist in zwitterionic form. The present invention includes each zwitterionic form of compounds of the invention, and mixtures thereof.

As used herein the term "pro-drug" refers to an agent, which is converted into the parent drug in vivo by some physiological chemical process (e.g., a prodrug on being brought to the physiological pH is converted to the desired drug form). Pro-drugs are often useful because, in some situations, they may be easier to administer than the parent drug. They may, for instance, be bioavailable by oral administration whereas the parent drug is not. The prodrug may also have improved solubility in pharmacological compositions over the parent drug. An example, without limitation, of a pro-drug would be a compound of the present invention wherein it is administered as an ester (the "pro-drug") to facilitate transmittal across a cell membrane where water solubility is not beneficial, but then it is metabolically hydrolyzed to the carboxylic acid once inside the cell where water solubility is beneficial. Pro-drugs have many useful properties. For example, a pro-drug may be more water soluble than the ultimate drug, thereby facilitating intravenous administration of the drug. A pro-drug may also have a higher level of oral bioavailability than the ultimate drug. After administration, the prodrug is enzymatically or chemically cleaved to deliver the ultimate drug in the blood or tissue.

Exemplary pro-drugs release an amine of a compound of the invention wherein the free hydrogen of an amine or alcohol is replaced by $(C_1\text{-}C_6)$alkanoyloxymethyl, 1-((C_1-C_6)alkanoyloxy)ethyl, 1-methyl-1-((C_1-C_6)alkanoyloxy)ethyl, (C_1-C_6)alkoxycarbonyloxymethyl, N—(C_1-C_6)alkoxycarbonylamino-methyl, succinoyl, (C_1-C_6)alkanoyl, α-amino (C_1-C_4)alkanoyl, arylactyl and α-aminoacyl, or α-aminoacyl-α-aminoacyl wherein said α-aminoacyl moieties are independently any of the naturally occurring L-amino acids found in proteins, —P(O)$(OH)_2$, —P(O)(O(C_1-C_6)alkyl)$_2$ or glycosyl (the radical resulting from detachment of the hydroxyl of the hemiacetal of a carbohydrate).

Other exemplary pro-drugs upon cleavage release a corresponding free acid, and such hydrolyzable ester-forming residues of the compounds of this invention include but are not limited to carboxylic acid substituents (e.g., —(CH_2)C(O)OH or a moiety that contains a carboxylic acid) wherein the free hydrogen is replaced by (C_1-C_4)alkyl, (C_2-C_{12})alkanoyloxymethyl, (C_4-C_9)1-(alkanoyloxy)ethyl, 1-methyl-1-(alkanoyloxy)-ethyl having from 5 to 10 carbon atoms, alkoxycarbonyloxymethyl having from 3 to 6 carbon atoms, 1-(alkoxycarbonyloxy)ethyl having from 4 to 7 carbon atoms, 1-methyl-1-(alkoxycarbonyloxy)ethyl having from 5 to 8 carbon atoms, N-(alkoxycarbonyl)aminomethyl having from 3 to 9 carbon atoms, 1-(N-(alkoxycarbonyl)amino)ethyl having from 4 to 10 carbon atoms, 3-phthalidyl, 4-crotonolactonyl, gamma-butyrolacton-4-yl, di-N,N—(C_1-C_2)alkylamino(C_2-C_3)alkyl (such as β-dimethylaminoethyl), carbamoyl-(C_1-C_2)alkyl, N,N-di(C_1-C_2)-alkylcarbamoyl-(C_1-C_2)alkyl and piperidino-, pyrrolidino- or morpholino(C_2-C_3) alkyl.

The term "subject" as used herein, refers to an animal, typically a mammal or a human, that will be or has been the object of treatment, observation, and/or experiment. When the term is used in conjunction with administration of a compound or drug, then the subject has been the object of treatment, observation, and/or administration of the compound or drug.

The terms "co-administration" and "co-administering" refer to both concurrent administration (administration of two or more therapeutic agents at the same time) and time varied administration (administration of one or more therapeutic agents at a time different from that of the administration of an additional therapeutic agent or agents), as long as the therapeutic agents are present in the patient to some extent at the same time.

The term "therapeutically effective amount" as used herein, means that amount of active compound or pharmaceutical agent that elicits a biological or medicinal response in a cell culture, tissue system, animal, or human that is being sought by a researcher, veterinarian, clinician, or physician, which includes alleviation of the symptoms of the disease, condition, or disorder being treated.

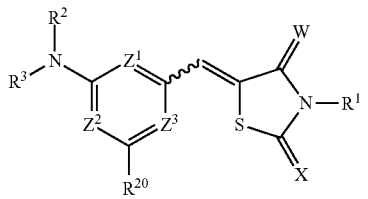
The term "composition" is intended to encompass a product comprising the specified ingredients in the specified amounts, as well as any product that results, directly or indirectly, from combinations of the specified ingredients in the specified amounts.

The term "pharmaceutically acceptable carrier" refers to a medium that is used to prepare a desired dosage form of a compound. A pharmaceutically acceptable carrier can include one or more solvents, diluents, or other liquid vehicles; dispersion or suspension aids; surface active agents; isotonic agents; thickening or emulsifying agents; preservatives; solid binders; lubricants; and the like. Remington's Pharmaceutical Sciences, Fifteenth Edition, E. W. Martin (Mack Publishing Co., Easton, Pa., 1975) and Handbook of Pharmaceutical Excipients, Third Edition, A. H. Kibbe ed. (American Pharmaceutical Assoc. 2000), disclose various carriers used in formulating pharmaceutical compositions and known techniques for the preparation thereof.

Compounds

An aspect of the invention relates to a compound of formula 1:

1



or a pharmaceutically acceptable salt thereof, wherein independently for each occurrence:

W and X are independently oxygen or sulfur;

Z^1, Z^2 and Z^3 are independently C—R^{20} or N, provided that at least one of Z^1 and Z^2 is N;

R^1 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl, heterocyclyl, aralkyl, heteroaralkyl, heterocyclylalkyl, —COR^6, —$C(O)OR^6$, —$SO_2(R^6)$, —$C(O)N(R^6)(R^7)$, —$SO_2N(R^6)(R^7)$, and —$[C(R^4)_2]_p$—R^5;

R^2 and R^3 are each independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl, heterocyclyl, aralkyl, heteroaralkyl, heterocyclylalkyl, —$[C(R^4)_2]_p$—R^5, —COR^6, —$C(O)OR^6$, —$SO_2(R^6)$, —$C(O)N(R^6)(R^7)$, —$SO_2N(R^6)(R^7)$, —$P(O)(OR^6)(OR^7)$; or R^2 and R^3 are joined together to form an optionally substituted heterocyclic ring;

R^4 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, heterocyclylalkyl, aralkyl, heteroaryl, heteroaralkyl, halo, hydroxy, alkoxy, hydroxyalkyl, and alkoxyalkyl;

R^5 is selected from the group consisting of aryl, heteroaryl, heterocyclyl, —$N(R^8)(R^9)$, —$N(R^8)COR^9$, —$N(R^8)C(O)OR^9$, —$N(R^8)SO_2(R^9)$, —$CON(R^8)(R^9)$, —$OC(O)N(R^8)$—(R^9), —$SO_2N(R^8)(R^9)$, —$OC(O)OR^8$, —$COOR^S$, —$C(O)N(OH)(R^8)$, —$OS(O)_2OR^8$, —$S(O)_2OR^8$, —$S(O)_2R^8$, —OR^8, —COR^8, —$OP(O)(OR^8)(OR^8)$, —$P(O)(OR^8)(OR^8)$ and —$N(R^8)P(O)(OR^9)(OR^9)$;

R^6 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl, heterocyclyl, aralkyl, heteroaralkyl, and heterocyclylalkyl;

R^7 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl, heterocyclyl, aralkyl, heteroaralkyl, and heterocyclylalkyl; or R^6 and R^7 are joined together to form a heterocyclic ring;

R^8 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl, heterocyclyl, aralkyl, heteroaralkyl, and heterocyclylalkyl;

R^9 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl, heterocyclyl, aralkyl, heteroaralkyl, and heterocyclylalkyl; or R^8 and R^9 are joined together to form a heterocyclic ring;

R^{20} is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl, heterocyclyl, aralkyl, heteroaralkyl, heterocyclylalkyl, halo, haloalkyl, trifluoromethyl, fluoroalkyl, perfluoroalkyl, thio, cyano, hydroxy, methoxy, alkoxy, phenoxy, aryloxy, heteroaryloxy, carboxyl, alkoxycarbonyl, acyl, nitro, amino, alkylamino, arylamino, heteroarylamino, amido, acylamino, sulfate, sulfonate, sulfonyl, sulfoxido, sulfonamido, sulfamoyl, —$[C(R^4)_2]_p$—R^5, $NR^{14}R^{15}$, OR^{16}, O—$[C(R^4)_2]_p$—R^5, NR^{14}—$[C(R^4)_2]_p$—R^5 and SR^{16};

R^{14} and R^{15} are each independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl, heterocyclyl, aralkyl, heteroaralkyl, heterocyclylalkyl, —$[C(R^4)_2]$—R^5, —COR^6, —$C(O)OR^6$, —$SO_2(R^6)$, —$C(O)N(R^6)(R^7)$, —$SO_2N(R^6)(R^7)$, and —$P(O)(OR^6)(OR^7)$; or R^{14} and R^{15} are joined together to form an optionally substituted heterocyclic ring;

R^{16} is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl, heterocyclyl, aralkyl, heteroaralkyl, heterocyclylalkyl, —$[C(R^4)_2]_p$—R^5, —COR^6, and —$C(O)N(R^6)(R^7)$; and

p is 1, 2, 3, 4, 5, or 6;

wherein any one of the aforementioned alkyl, alkenyl, alkynyl, aryl, heteroaryl, heterocyclyl, aralkyl, heteroaralkyl, and heterocyclylalkyl may be optionally substituted.

In one embodiment, W and X are oxygen.

In one embodiment, Z^1 and Z^2 are nitrogen; and Z^3 is C—R^{20}.

In one embodiment, Z^1, Z^2 and Z^3 are nitrogen.

In one embodiment, Z^1 is nitrogen; and Z^2 and Z^3 are each C—R^{20}.

In one embodiment, Z^2 is nitrogen; and Z^1 and Z^3 are each C—R^{20}.

In one embodiment, R^1 is hydrogen.

In one embodiment, R^1 is selected from the group consisting of alkyl, alkenyl, alkynyl, aryl, heteroaryl, heterocyclyl, and —$[C(R^4)_2]_p$—R^5.

In one embodiment, W and X are oxygen, Z^1 and Z^2 are each nitrogen, Z^3 is C—R^{20} and R^1 is hydrogen.

In one embodiment, R^2 and R^3 are joined together to form an optionally substituted heterocyclic ring.

In one embodiment, the optionally substituted heterocyclic ring is selected from the group consisting of piperazinyl, homopiperizinyl, pyrrolidinyl, piperidinyl, homopiperidinyl, morpholinyl, 1,4-diazepan-5-onyl and quinolinyl.

In one embodiment, R^2 and R^3 are independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl, heterocyclyl, —$[C(R^4)_2]_p$—R^5, —COR^6, —$C(O)OR^6$, —$SO_2(R^6)$, —$C(O)N(R^6)(R^7)$, and —$SO_2N(R^6)(R^7)$, wherein the alkyl, alkenyl, alkynyl, aryl, heteroaryl, and heterocyclyl may be optionally substituted.

In one embodiment, R^2 is —$[C(R^4)_2]_p$—R^5, and R^3 is selected from the group consisting of alkyl, alkenyl, alkynyl, aryl, heteroaryl, heterocyclyl, —COR^6, —$C(O)OR^6$, —$SO_2(R^6)$, —$C(O)N(R^6)(R^7)$, and —$SO_2N(R^6)(R^7)$, wherein the alkyl, alkenyl, alkynyl, aryl, heteroaryl, and heterocyclyl may be optionally substituted.

In one embodiment, R^5 is aryl or heteroaryl, each of which may be optionally substituted.

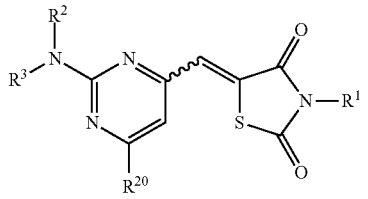
In one embodiment, R^5 is —$N(R^8)(R^9)$.

In one embodiment, R^4 is hydrogen.

In one embodiment, R^{20} is selected from the group consisting of alkyl, alkenyl, alkynyl, aryl, heteroaryl, heterocyclyl, halo, haloalkyl, trifluoromethyl, carboxyl, alkoxycarbonyl, acyl, nitro, amido, acylamino, sulfonamido, —$[C(R^4)_2]_p$—R^5; $NR^{14}R^{15}$, OR^{16}, and SR^{16}.

In one embodiment, R^{20} is hydrogen.

An aspect of the invention relates to compound of formula 2:



or a pharmaceutically acceptable salt thereof, wherein independently for each occurrence:

R^1 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl, heterocyclyl, aralkyl, heteroaralkyl, heterocyclylalkyl, —COR^6, —$C(O)OR^6$, —$SO_2(R^6)$, —$C(O)N(R^6)(R^7)$, —$SO_2N(R^6)(R^7)$, and —$[C(R^4)_2]_p$—R^5;

R^2 and R^3 are each independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl, heterocyclyl, aralkyl, heteroaralkyl, heterocyclylalkyl, —$[C(R^4)_2]_p$—R^5, —COR^6, —$C(O)OR^6$, —$SO_2(R^6)$, —$C(O)N(R^6)(R^7)$, —$SO_2N(R^6)(R^7)$—$P(O)(OR^6)(OR^7)$; or R^2 and R^3 are joined together to form an optionally substituted heterocyclic ring;

R^4 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, heterocyclylalkyl, aralkyl, heteroaryl, heteroaralkyl, halo, hydroxy, alkoxy, hydroxyalkyl, and alkoxyalkyl;

R^5 is selected from the group consisting of aryl, heteroaryl, heterocyclyl, —$N(R^8)(R^9)$, —$N(R^8)COR^9$, —$N(R^8)C(O)OR^9$, —$N(R)SO_2(R^9)$, —$CON(R^8)(R^9)$, —$OC(O)N(R^8)$—(R^9), —$SO_2N(R^8)(R^9)$, —$OC(O)OR^8$, —$COOR^8$, —$C(O)N(OH)(R^8)$, —$OS(O)_2OR^8$, —$S(O)_2OR^8$, —$S(O)_2R^8$, —OR^8, —COR^8, —$OP(O)(OR^8)(OR^9)$, —$P(O)(OR^8)(OR^9)$ and —$N(R^8)P(O)(OR^9)(OR^9)$;

R^6 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl, heterocyclyl, aralkyl, heteroaralkyl, and heterocyclylalkyl;

R^7 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl, heterocyclyl, aralkyl, heteroaralkyl, and heterocyclylalkyl, or R^6 and R^7 are joined together to form a heterocyclic ring;

R^8 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl, heterocyclyl, aralkyl, heteroaralkyl, and heterocyclylalkyl;

R^9 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl, heterocyclyl, aralkyl, heteroaralkyl, and heterocyclylalkyl; or R^8 and R^9 are joined together to form a heterocyclic ring;

R^{20} is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl, heterocyclyl, aralkyl, heteroaralkyl, heterocyclylalkyl, halo, haloalkyl, trifluoromethyl, fluoroalkyl, perfluoroalkyl, thio, cyano, hydroxy, methoxy, alkoxy, phenoxy, aryloxy, heteroaryloxy, carboxyl, alkoxycarbonyl, acyl, nitro, amino, alkylamino, arylamino, heteroarylamino, amido, acylamino, sulfate, sulfonate, sulfonyl, sulfoxido, sulfonamido, sulfamoyl, —$[C(R^4)_2]_p$—R^5, $NR^{14}R^{15}$, OR^{16}, and SR^{16};

R^{14} and R^{15} are each independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl, heterocyclyl, aralkyl, heteroaralkyl, heterocyclylalkyl, —$[C(R^4)_2]_p$—R^5, —COR^6, —$C(O)OR^6$, —$SO_2(R^6)$, —$C(O)N(R^6)(R^7)$, —$SO_2N(R^6)(R^7)$, and —$P(O)(OR^6)(OR^7)$; or R^{14} and R^{15} are joined together to form an optionally substituted heterocyclic ring;

R^{16} is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl, heterocyclyl, aralkyl, heteroaralkyl, heterocyclylalkyl, —$[C(R^4)_2]_p$—R^5, —COR^6, and —$C(O)N(R^6)(R^7)$; and

p is 1, 2, 3, 4, 5, or 6;

wherein any one of the aforementioned alkyl, alkenyl, alkynyl, aryl, heteroaryl, heterocyclyl, aralkyl, heteroaralkyl, and heterocyclylalkyl may be optionally substituted.

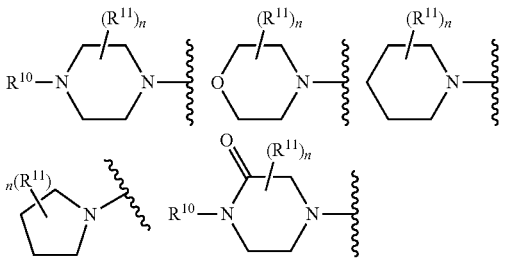
In one embodiment, R^1 is hydrogen.

In one embodiment, R^{20} is selected from the group consisting of hydrogen, alkyl, trifluoromethyl, alkenyl, alkynyl, aryl, heteroaryl, heterocyclyl, —$[C(R^4)_2]_p$—R^5, $NR^{14}R^{15}$, OR^{16}, and SR^{16}.

In one embodiment, R^{20} is hydrogen.

In one embodiment, R^2 and R^3 are joined together to form an optionally substituted heterocyclic ring.

In one embodiment, R^2 and R^3 are joined together to form an optionally substituted heterocyclic ring selected from the group consisting of:



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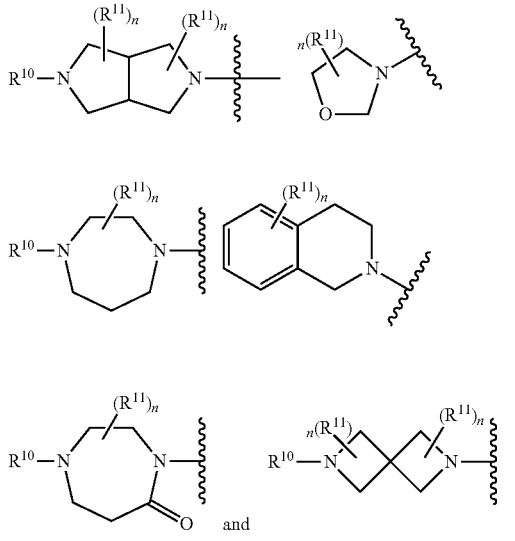


and

wherein, independently for each occurrence:

R^{10} is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl, heterocyclyl, aralkyl, heteroaralkyl, heterocyclylalkyl, —$[C(R^4)_2]_p$—R^5, —COR^{12}, —$C(O)OR^{12}$, —$SO_2(R^{12})$, —$C(O)N(R^{12})(R^{13})$, —$SO_2N(R^{12})(R^{13})$, —$P(O)(OR^{12})(OR^{13})$;

R^{12} and R^{13} are selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl, heterocyclyl, aralkyl, heteroaralkyl, and heterocyclylalkyl; or R^{12} and R^{13} are joined together to form a heterocyclic ring;

R^{11} is selected from the group consisting of alkyl, alkenyl, alkynyl, aryl, heteroaryl, heterocyclyl, halo, haloalkyl, thio, cyano, hydroxyalkyl, alkoxy, alkylalkoxy, alkylthio, nitro, cyano, —$N(R^{17})(R^{18})$, —$N(R^{17})COR^{18}$, —$N(R^{17})C(O)OR^{18}$, —$N(R^{17})SO_2(R^{18})$, —$CON(R^{17})(R^{18})$, —$OC(O)N(R^{17})$—(R^{18}), —$SO_2N(R^{17})(R^{18})$, —$OC(O)OR^{17}$, —$COOR^{17}$, —$C(O)N(OH)(R^{17})$, —$OS(O)_2OR^{17}$, —$S(O)_2OR^{17}$, —$S(O)_2R^{17}$, —OR^{17}, —COR^{17}, —$OP(O)(OR^{17})(OR^{18})$, —$P(O)(OR^{17})(OR^{18})$, —$N(R^{17})P(O)(OR^{18})(OR^{18})$, and —$[C(R^4)_2]_p$—$R^5$;

R^{17} and R^{18} selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl, heterocyclyl, aralkyl, heteroaralkyl, and heterocyclylalkyl; or R^{17} and R^{18} are joined together to form a heterocyclic ring; and

n is 0, 1, 2, or 3;

wherein any one of the aforementioned alkyl, alkenyl, alkynyl, aryl, heteroaryl, heterocyclyl, aralkyl, heteroaralkyl, and heterocyclylalkyl may be optionally substituted.

In one embodiment, R^{10} is selected from the group consisting of hydrogen, alkyl, aryl, heteroaryl, heterocyclyl, —$[C(R^4)_2]_p$—R^5, —COR^{12}, —$C(O)OR^{12}$, and —$SO_2(R^{12})$;

wherein any one of the aforementioned alkyl, aryl, heteroaryl, and heterocyclyl may be optionally substituted.

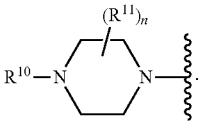
In one embodiment, n is 0.

In one embodiment, n is 1.

In one embodiment, R^{11} is selected from the group consisting of alkyl, heterocyclyl, cyano, hydroxyalkyl, —$N(R^{17})(R^{18})$, —$CON(R^{17})(R^{18})$, and —$[C(R^4)_2]^p$—R^5;

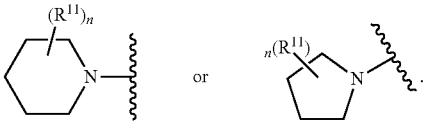
wherein any of the aforementioned alkyl and heterocyclyl may be optionally substituted.

In one embodiment, R^2 and R^3 are joined together to form an optionally substituted heterocyclic ring of the formula:



In one embodiment, n is 0 or 1.

In one embodiment, R^2 and R^3 are joined together to form an optionally substituted heterocyclic ring of the formula:



In one embodiment, R^2 and R^3 are independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl, heterocyclyl, —$[C(R^4)_2]_p$—R^5, —COR^6, —$C(O)OR^6$, —$SO_2(R^6)$, —$C(O)N(R^6)(R^7)$, and —$SO_2N(R^6)(R^7)$, wherein the alkyl, alkenyl, alkynyl, aryl, heteroaryl, and heterocyclyl may be optionally substituted.

In one embodiment, R^3 is —$[C(R^4)_2]_p$—R^5.

In one embodiment, R^2 is optionally substituted alkyl.

In one embodiment, R^4 is hydrogen.

In one embodiment, R^4 is hydroxy.

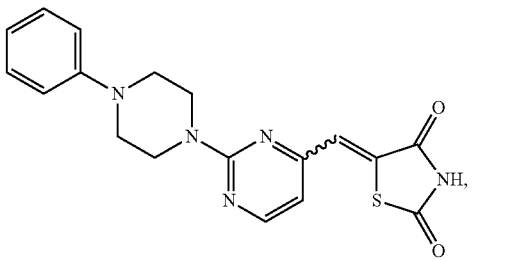
In one embodiment, R^5 is aryl, heteroaryl, heterocyclyl, each of which may be optionally substituted.

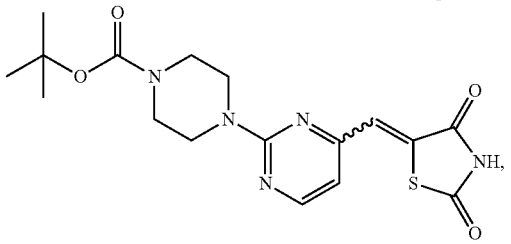
In one embodiment, p is 1, 2 or 3.

In one embodiment, R^5 is selected from the group consisting of —$N(R^8)(R^9)$, —$N(R^8)COR^9$, —$N(R^8)C(O)OR^9$, —$N(R^8)SO_2(R^9)$, —$CON(R^8)(R^9)$, —$OC(O)N(R^8)$—(R^9), —$SO_2N(R^8)(R^9)$, —$OC(O)OR^8$, —$COOR^9$, —$C(O)N(OH)(R^8)$, —$OS(O)_2OR^8$, —$S(O)_2OR^8$, —$S(O)_2R^8$, —OR^8, —COR^8, —$OP(O)(OR^8)(OR^8)$, —$P(O)(OR^8)(OR^8)$ and —$N(R^8)P(O)(OR^9)(OR^9)$.

In one embodiment, R^5 is —$N(R^8)(R^9)$.

An aspect of the invention relates to a compound, or a pharmaceutically acceptable salt thereof, selected from the group consisting of:





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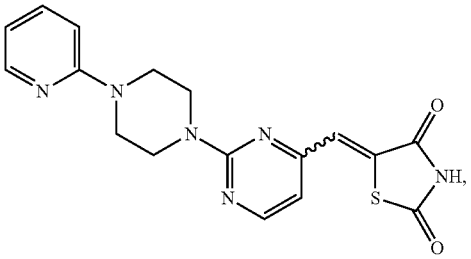

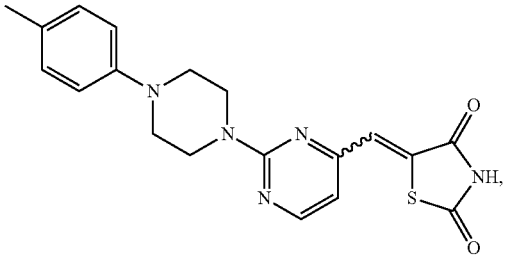

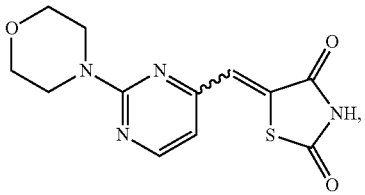

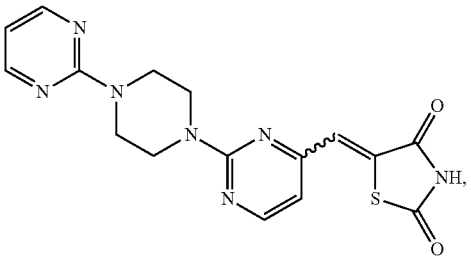

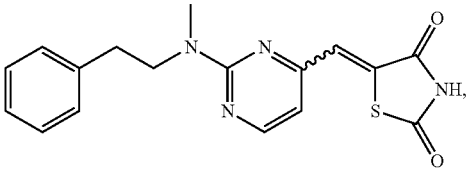

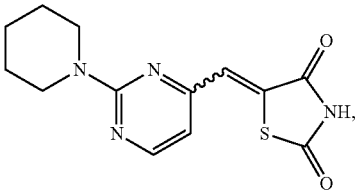

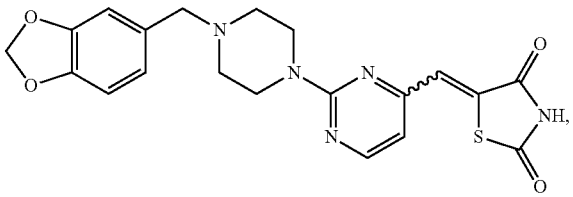

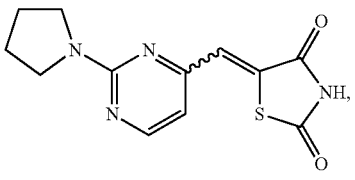

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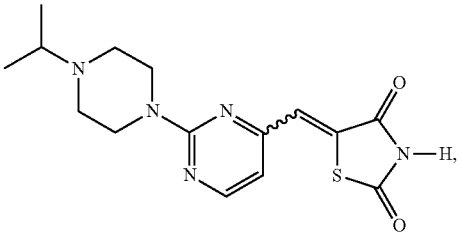

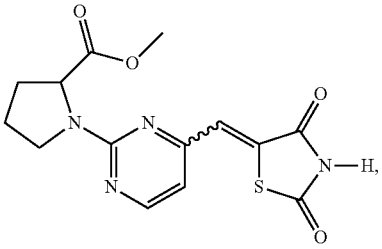

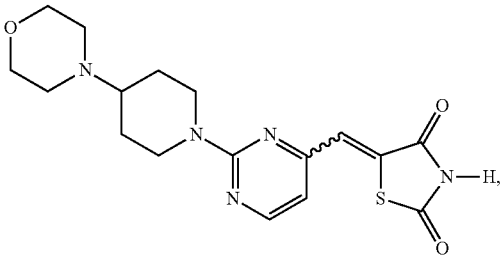

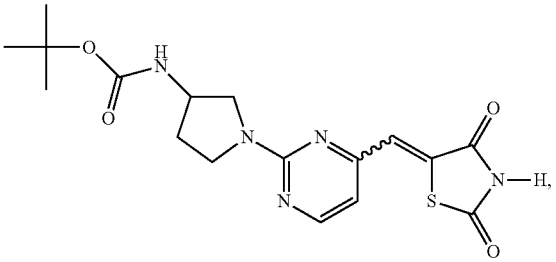

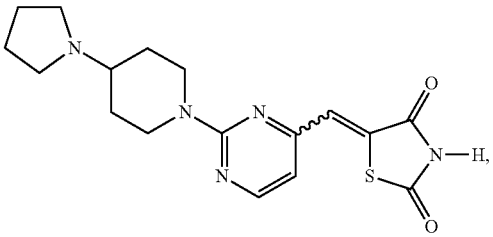

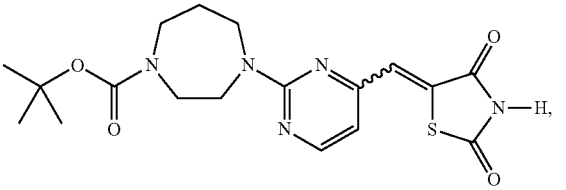

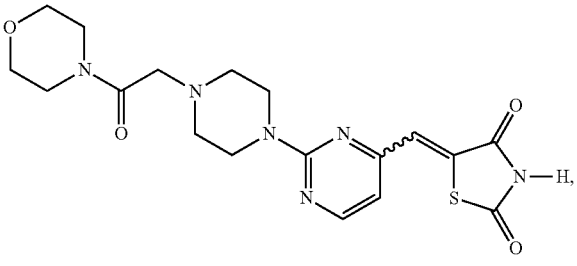

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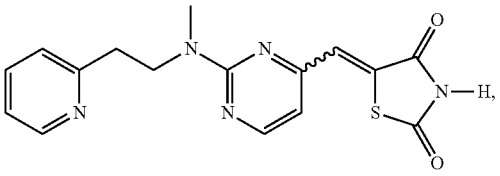

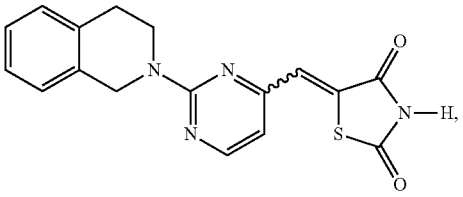

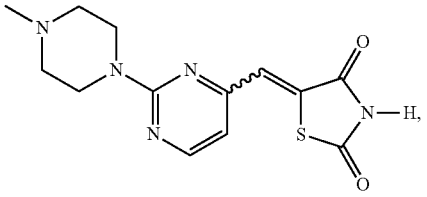

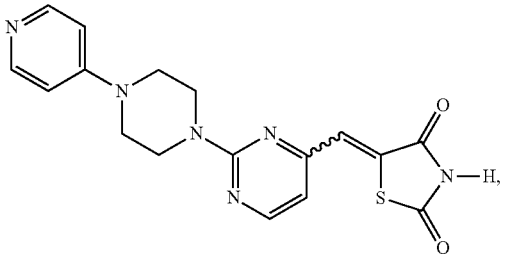

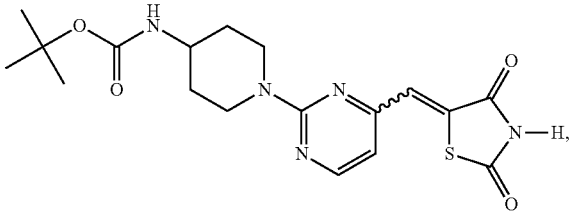

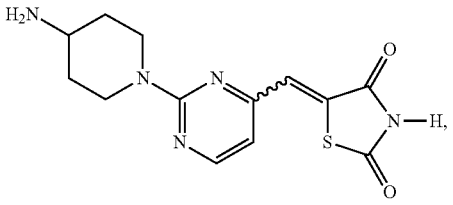

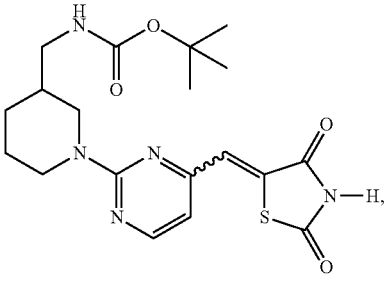

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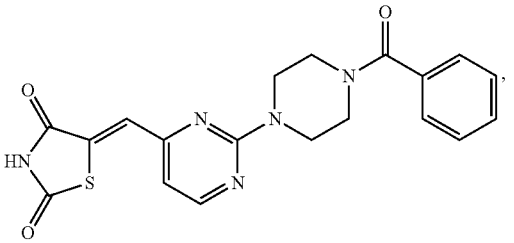

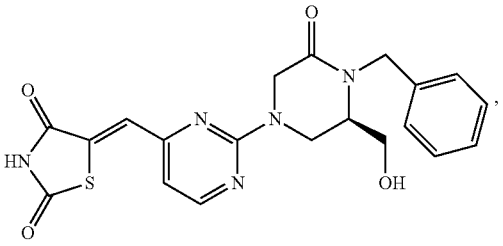

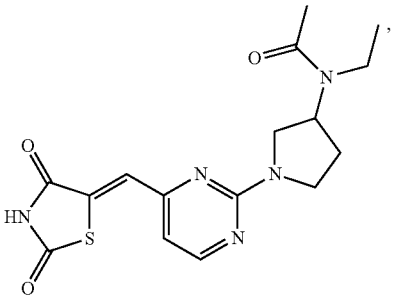

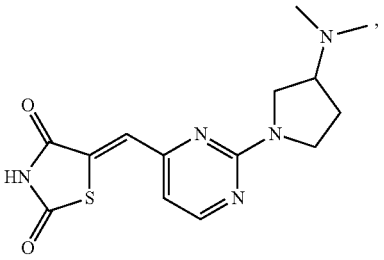

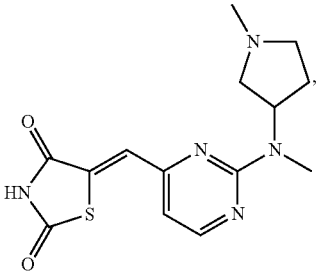

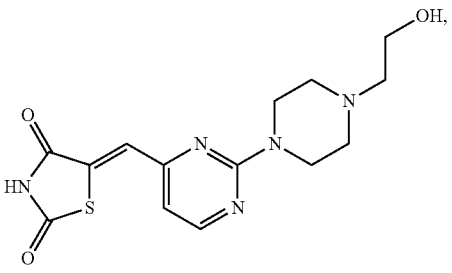

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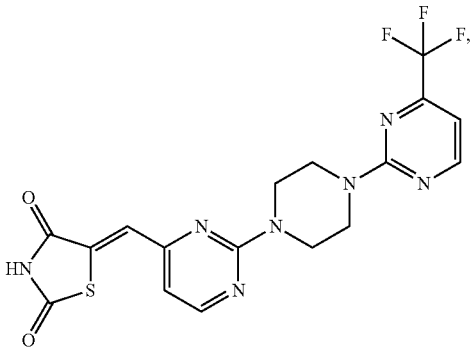

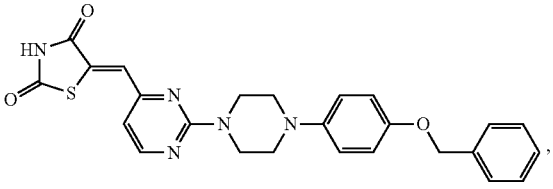

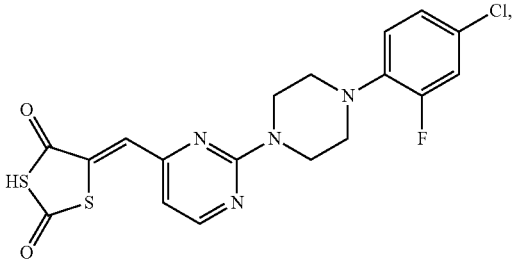

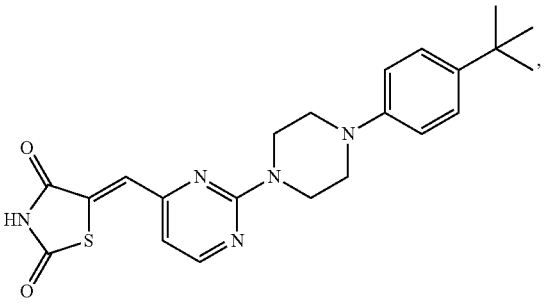

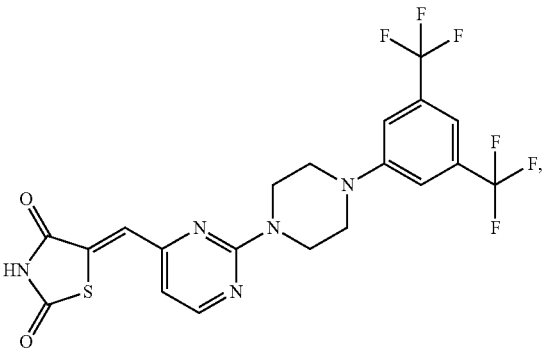

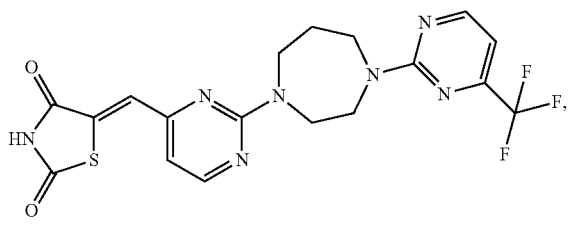

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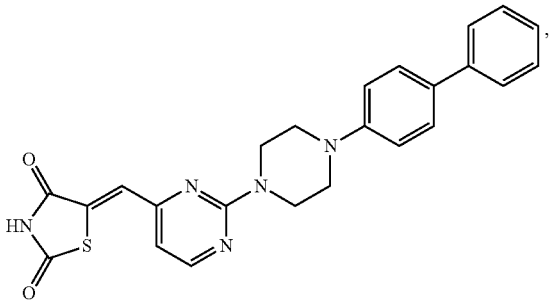

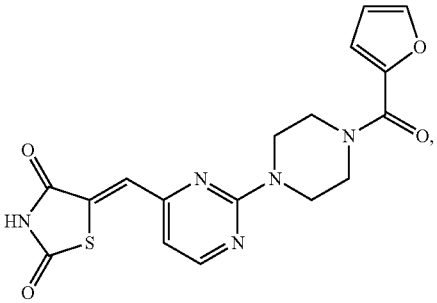

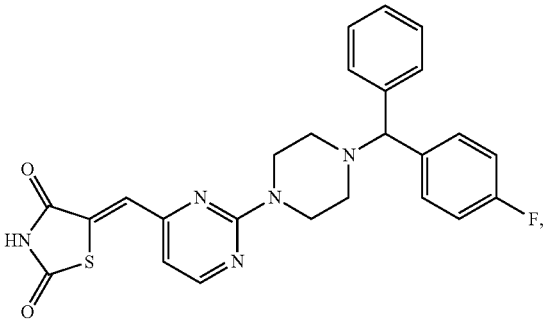

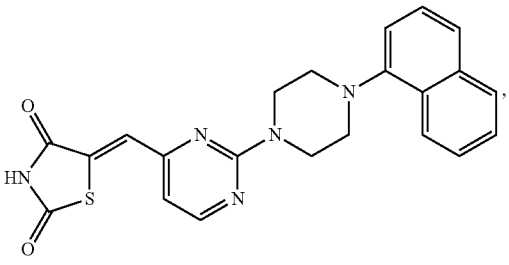

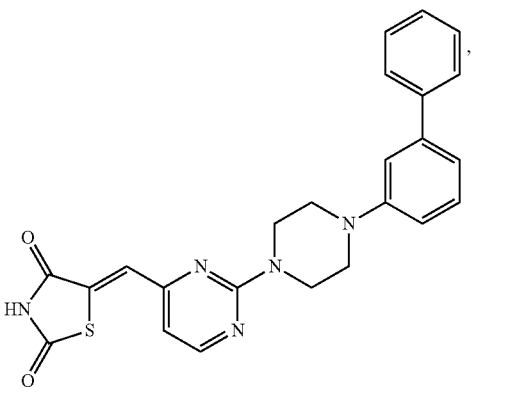

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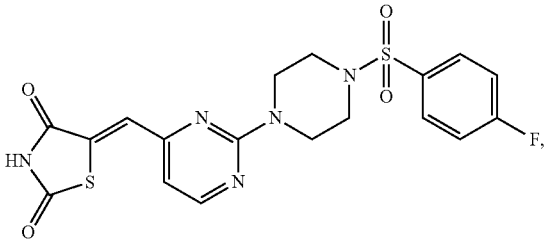

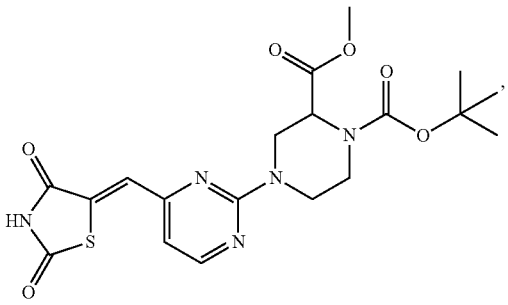

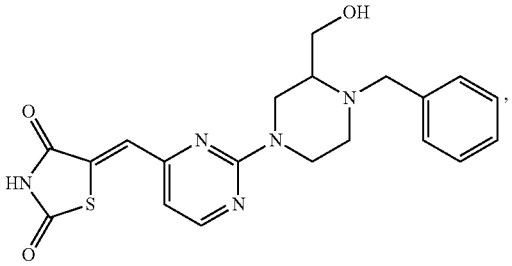

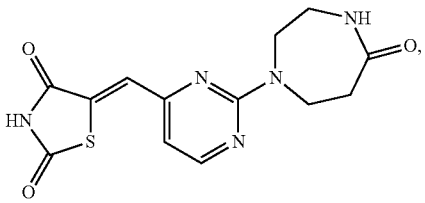

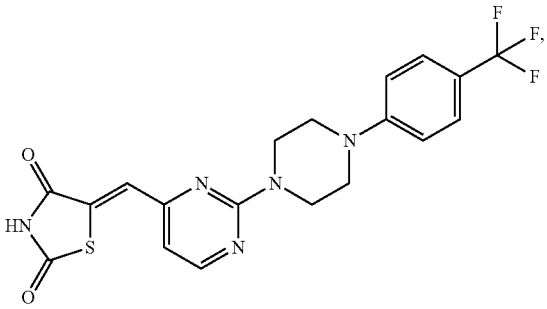

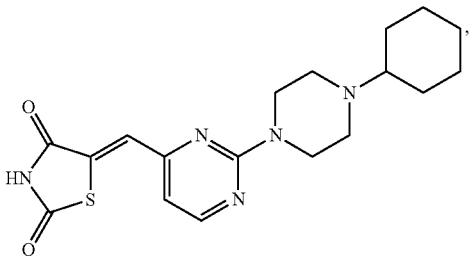

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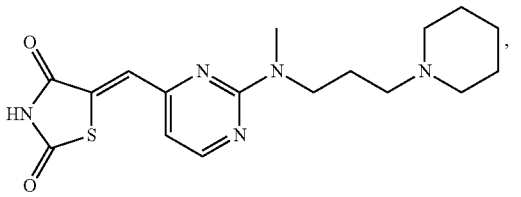

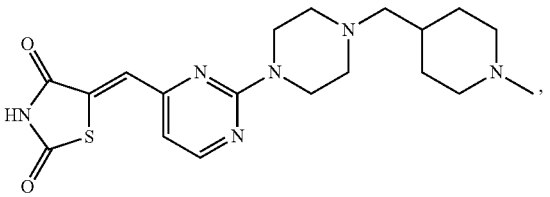

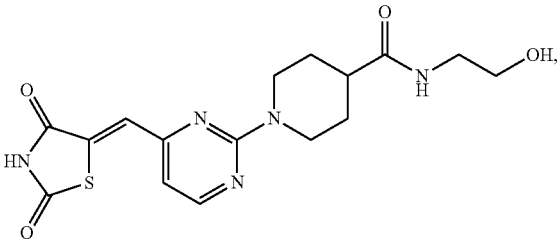

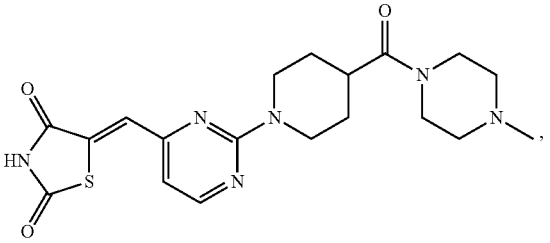

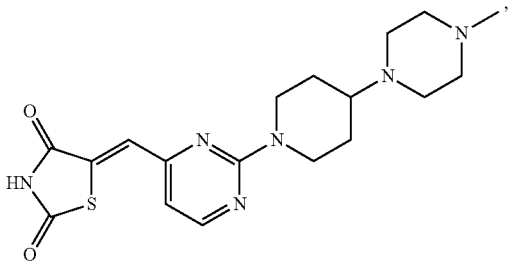

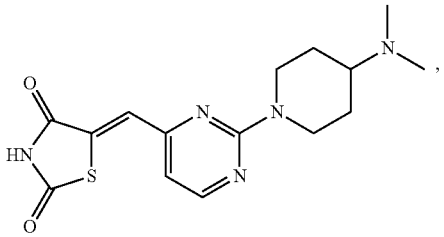

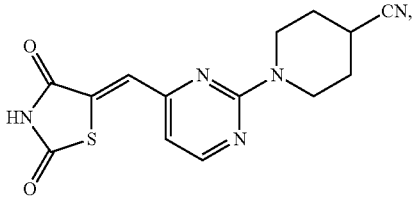

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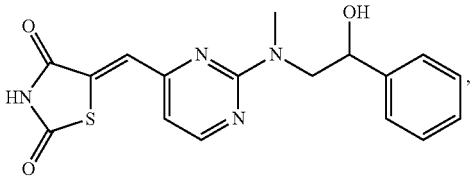

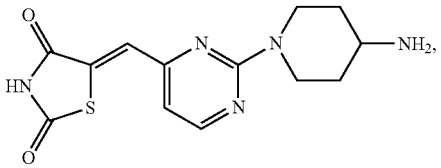

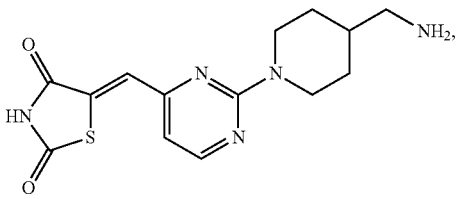

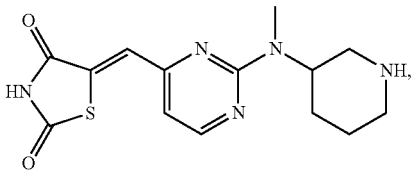

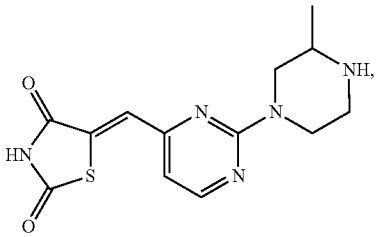

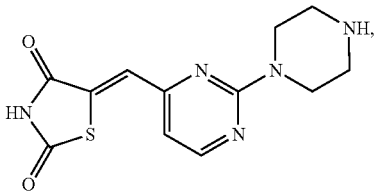

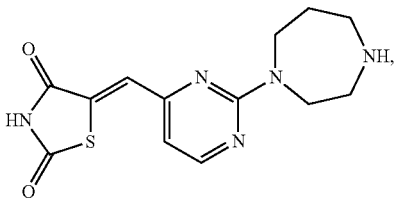

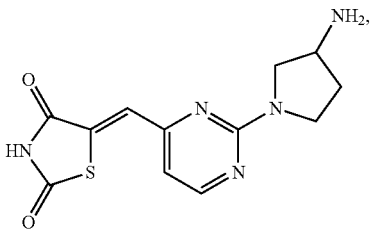

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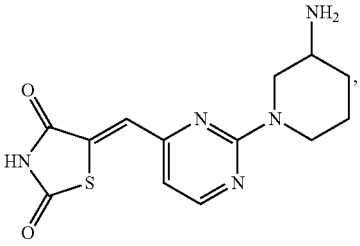

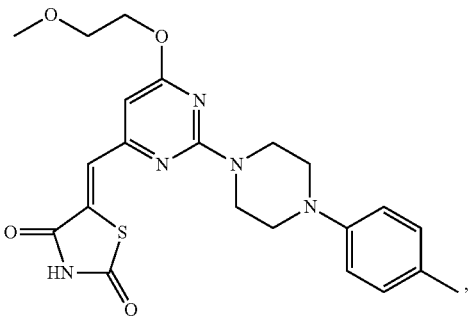

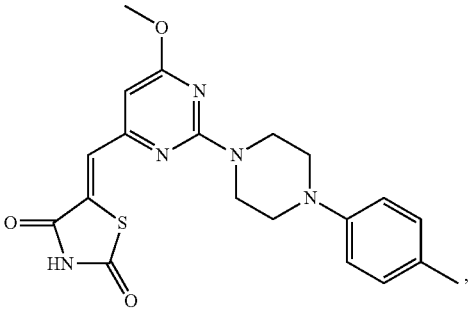

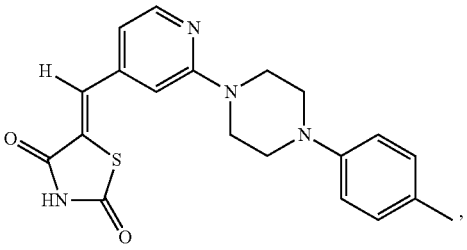

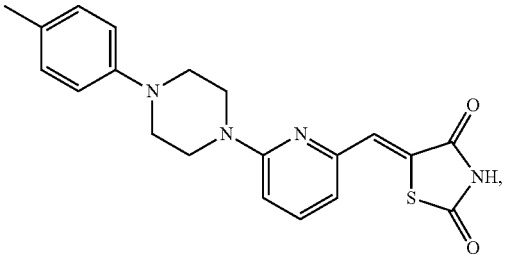

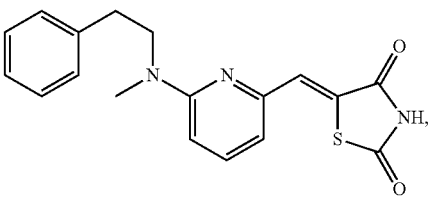

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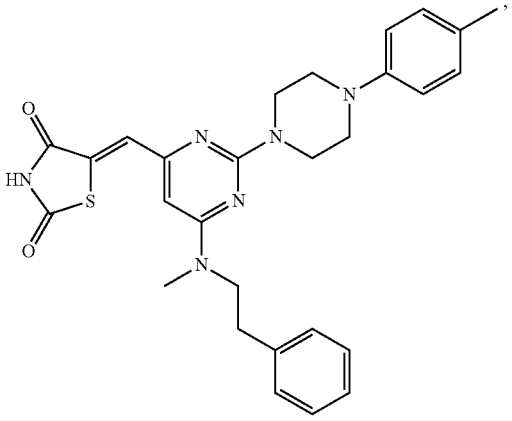

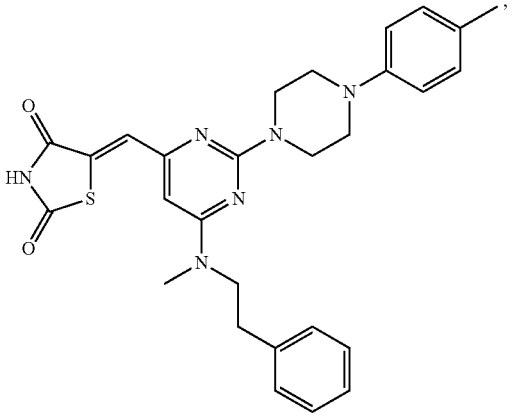

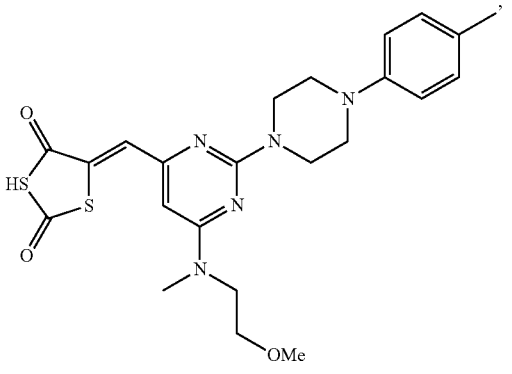

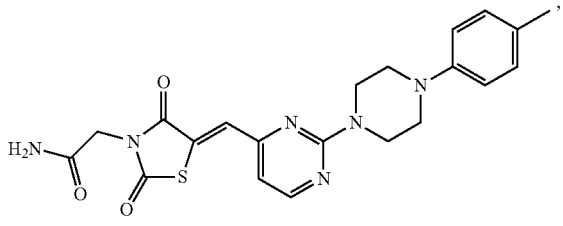

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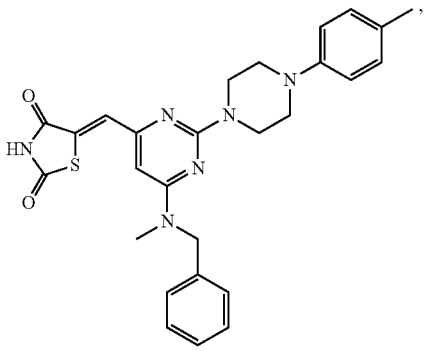

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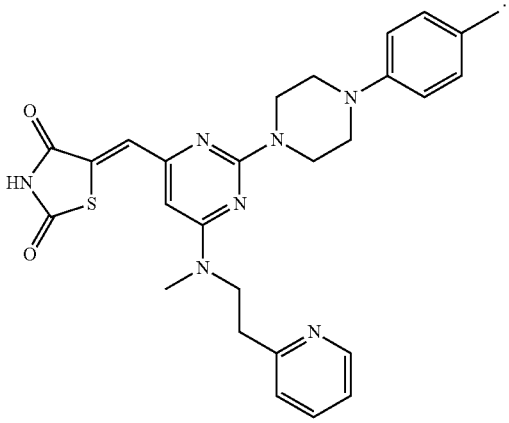
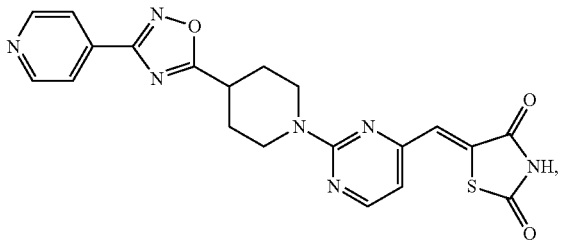
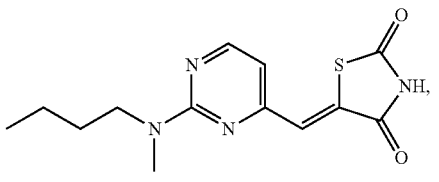
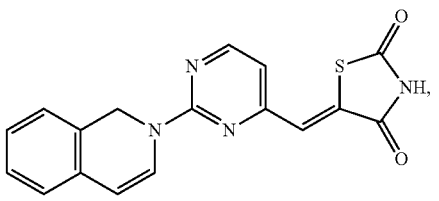


An aspect of the invention relates to a compound, or a pharmaceutically acceptable salt thereof, selected from the group consisting of:







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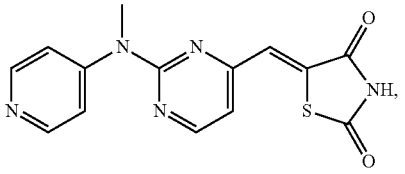

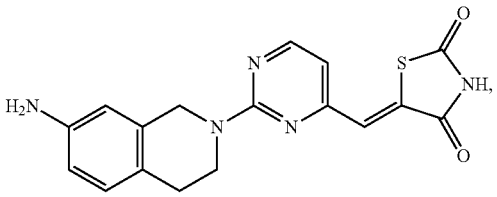

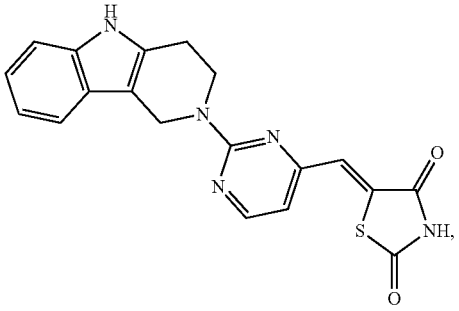

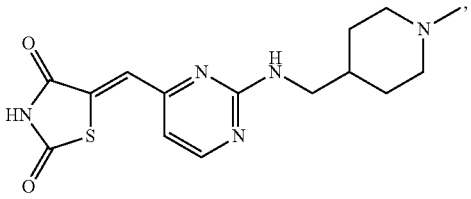

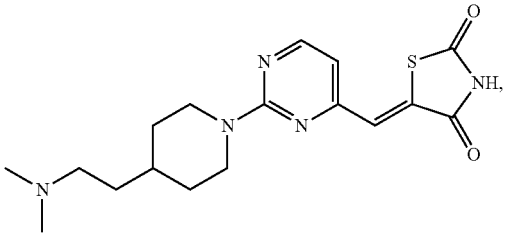

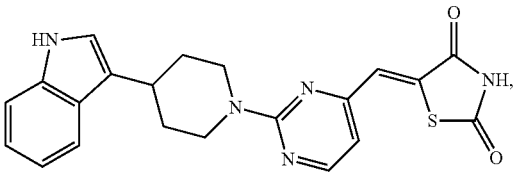

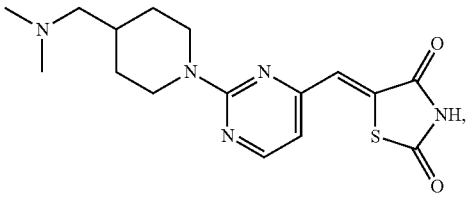

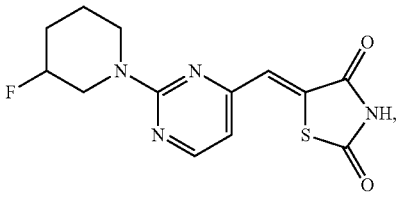

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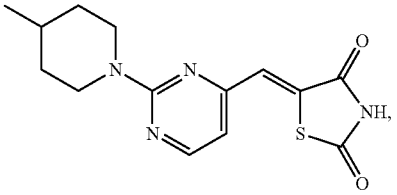

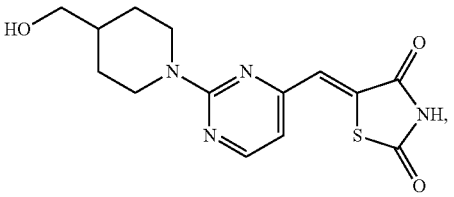

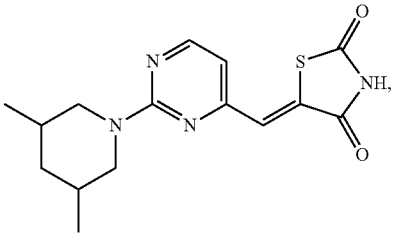

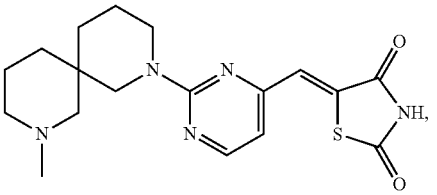

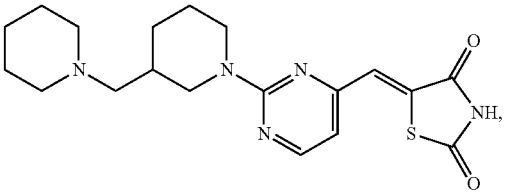

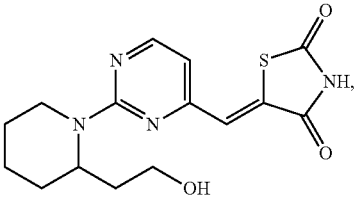

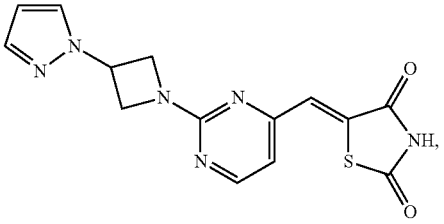

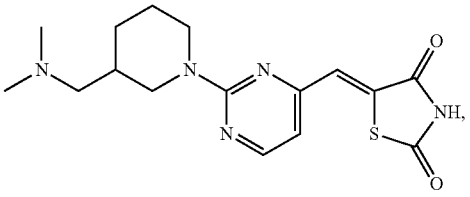

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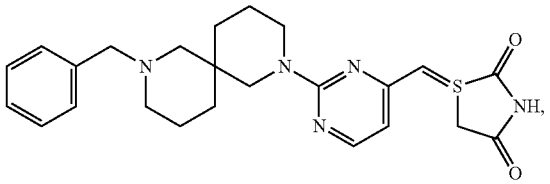

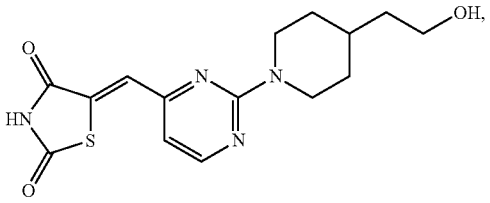

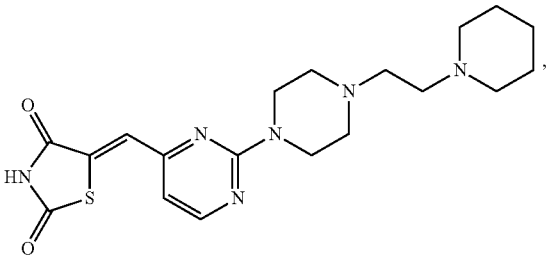

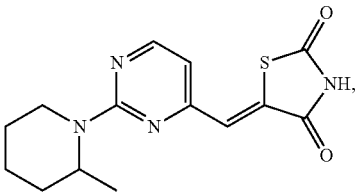

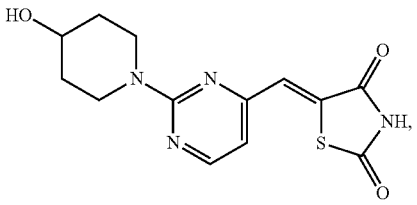

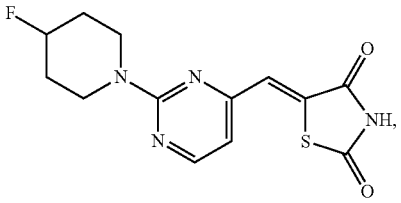

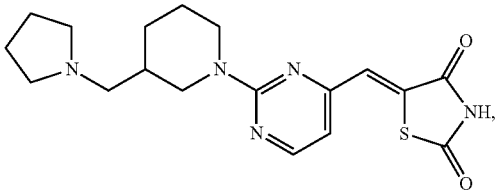

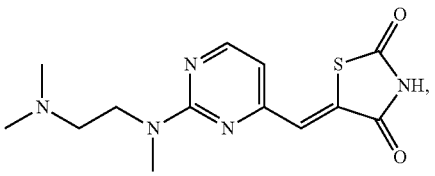

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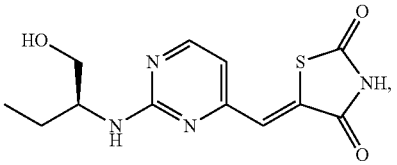

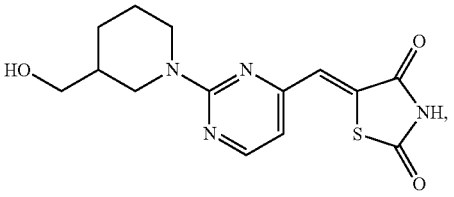

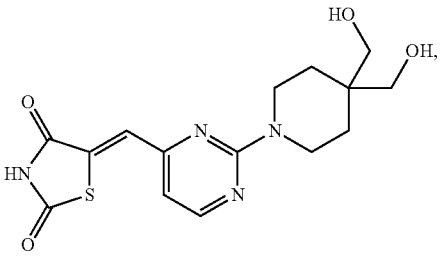

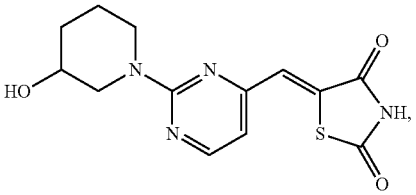

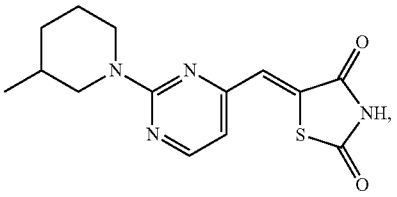

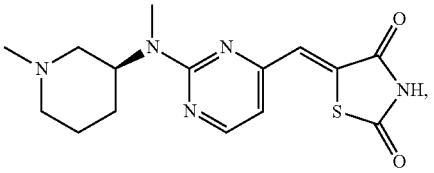

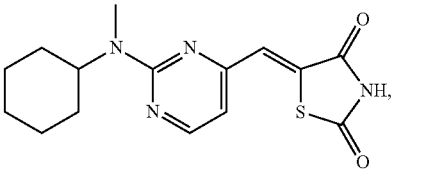

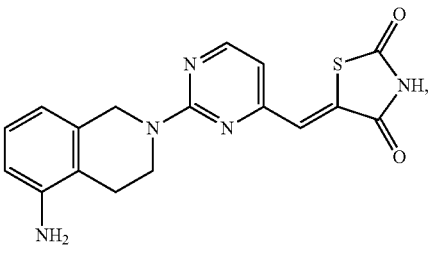

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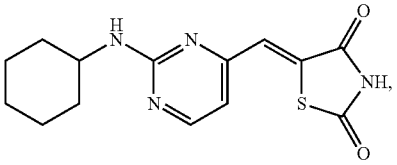

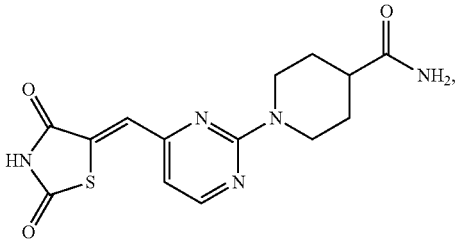

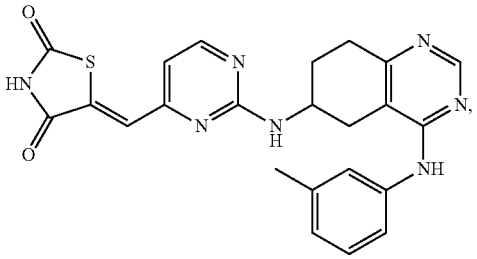

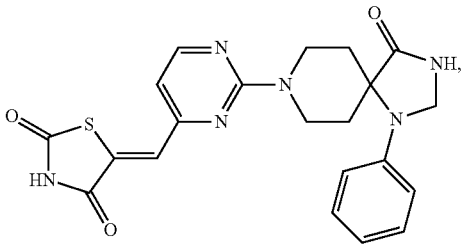

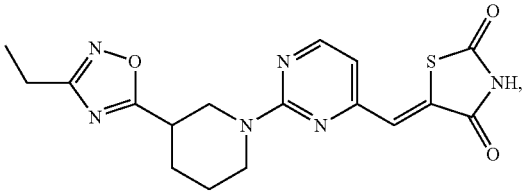

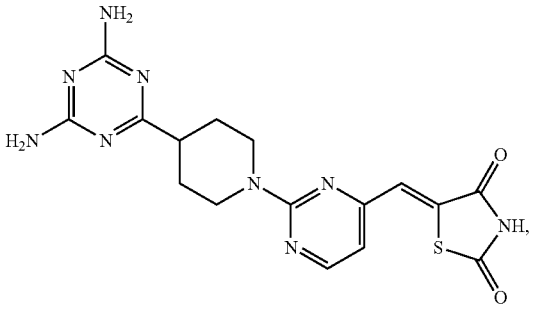

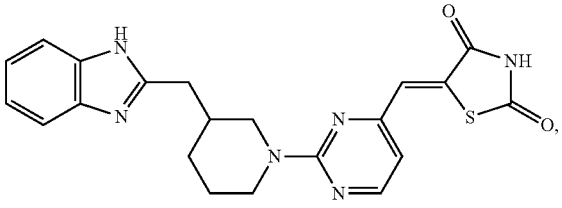

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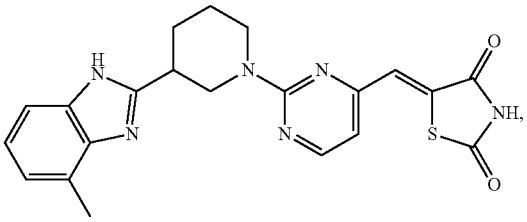

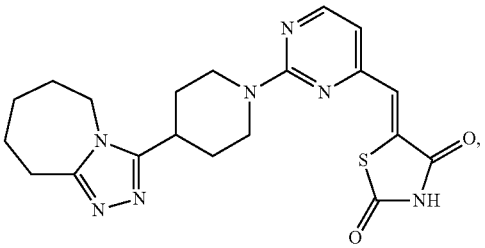

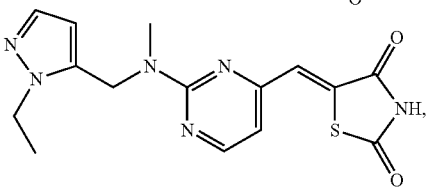

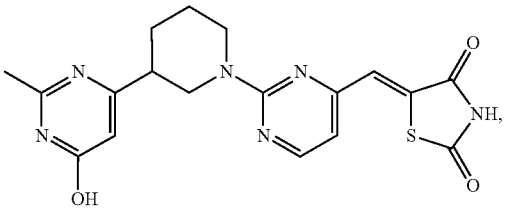

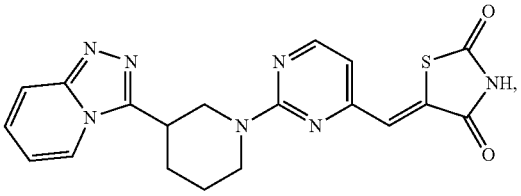

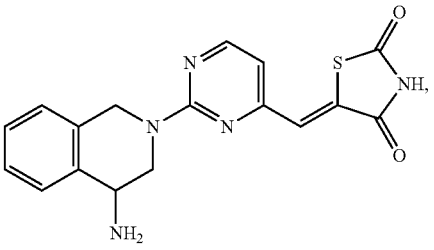

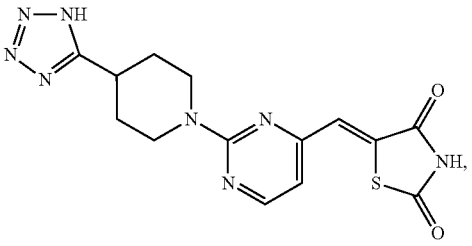

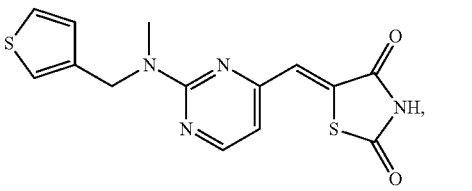

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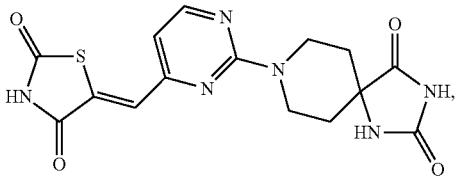

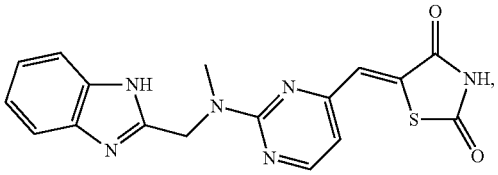

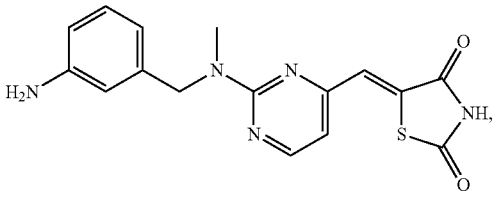

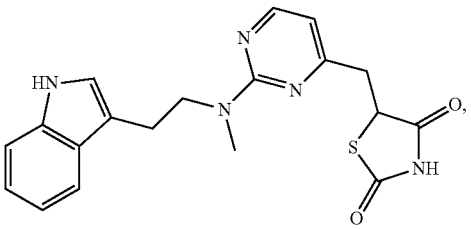

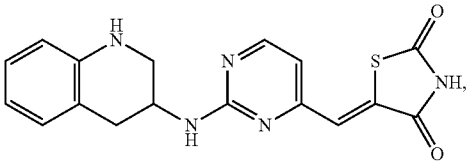

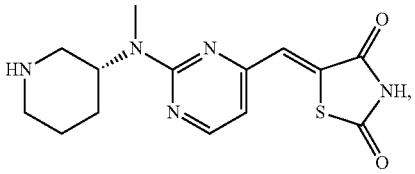

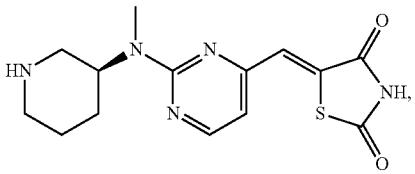

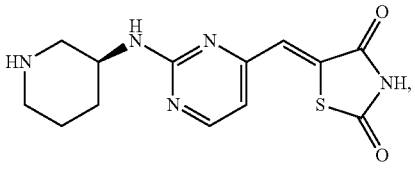

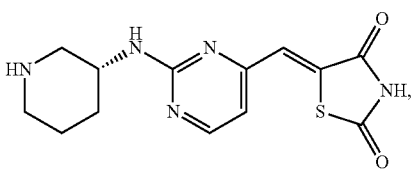

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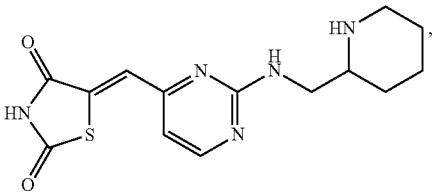

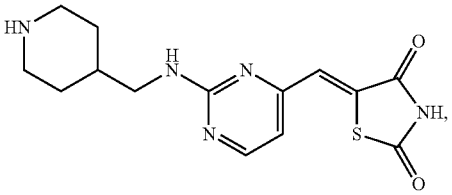

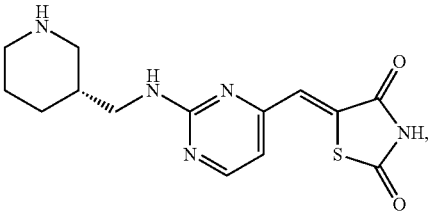

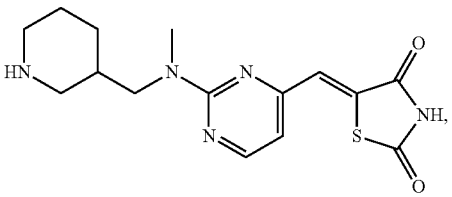

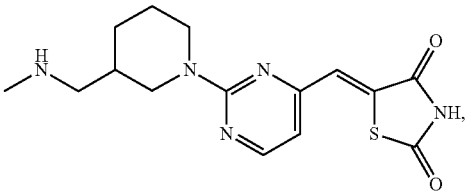

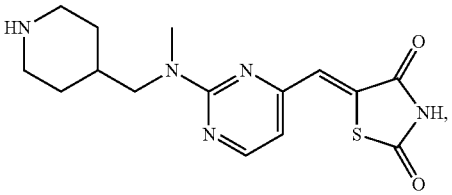

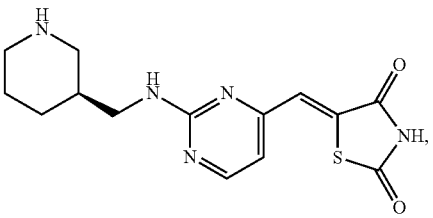

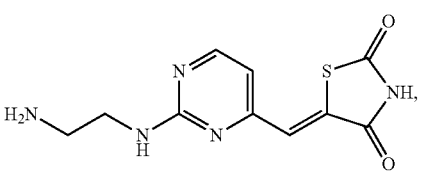

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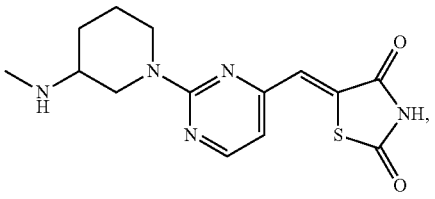

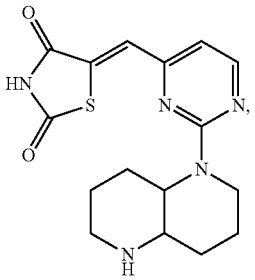

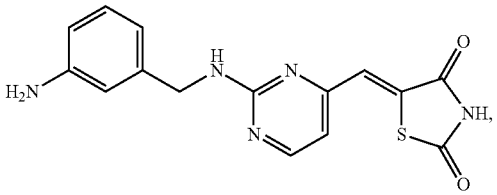

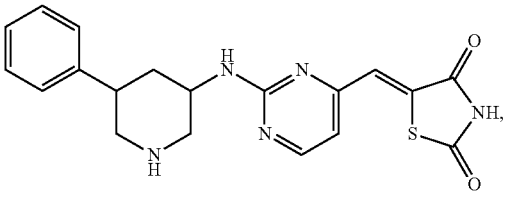

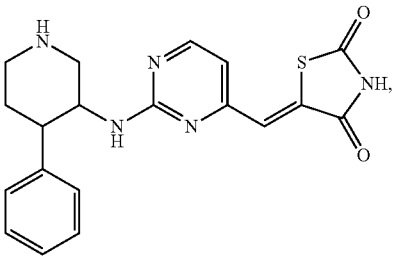

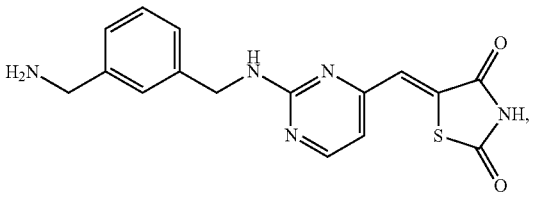

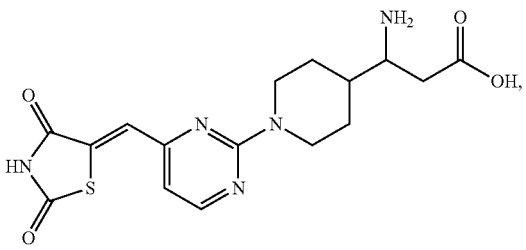

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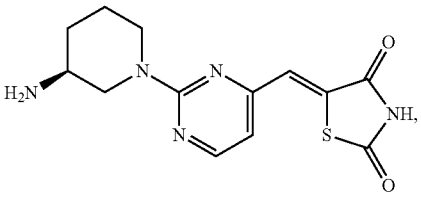

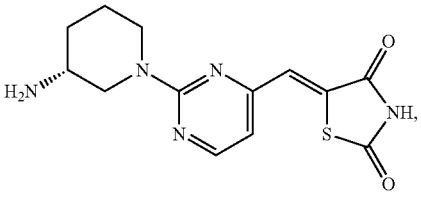

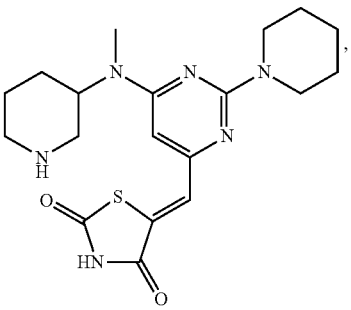

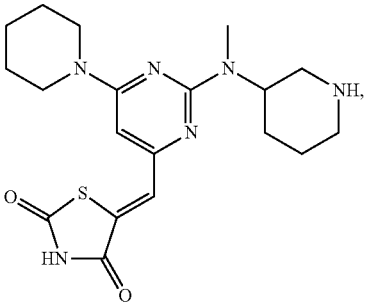

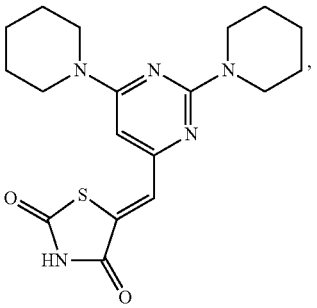

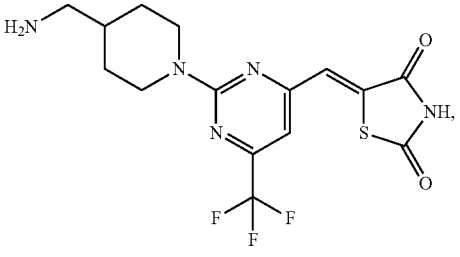

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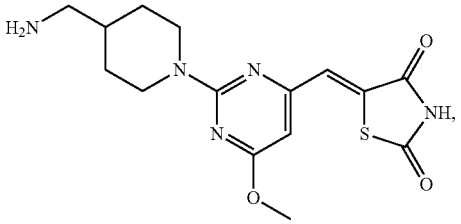

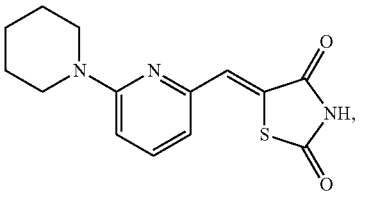

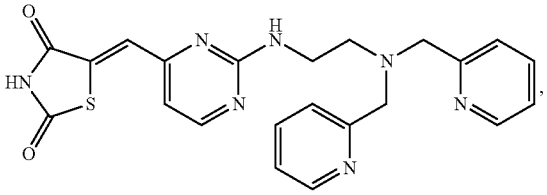

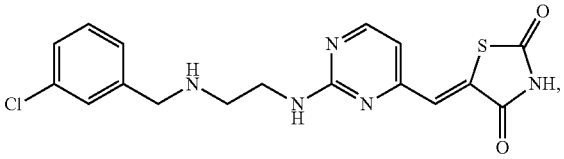

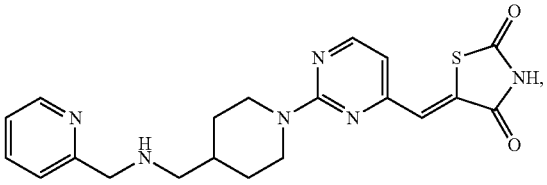

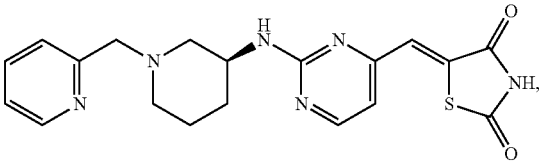

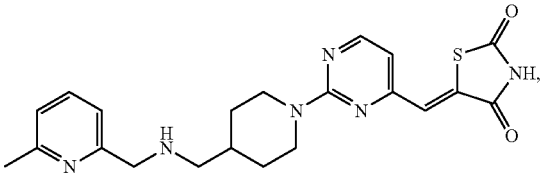

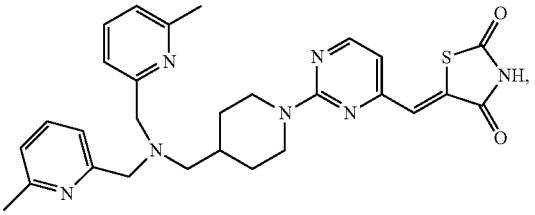

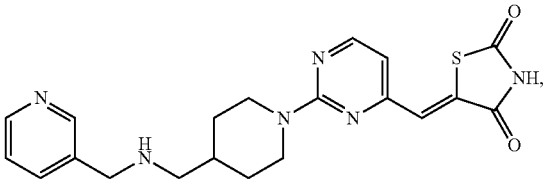

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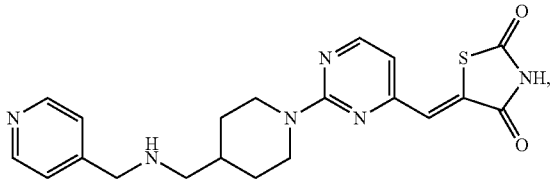

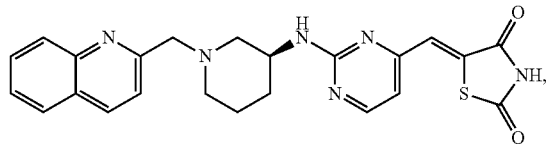

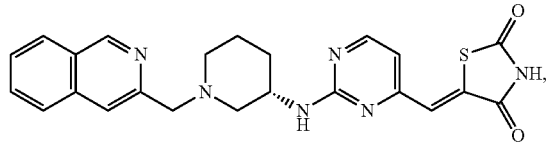

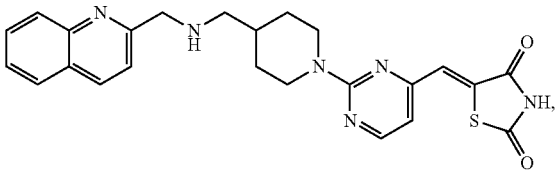

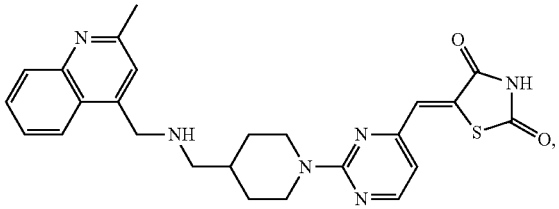

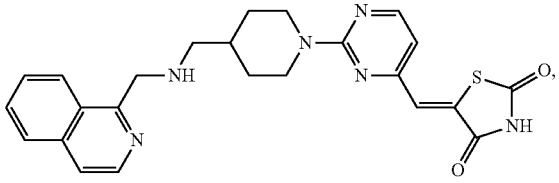

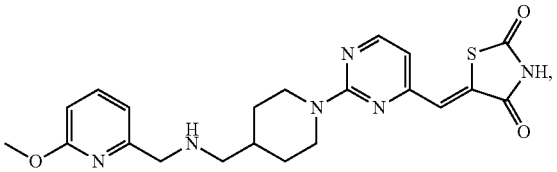

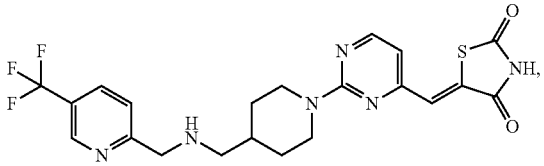

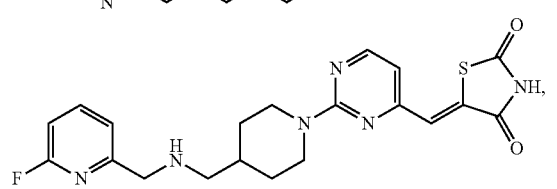

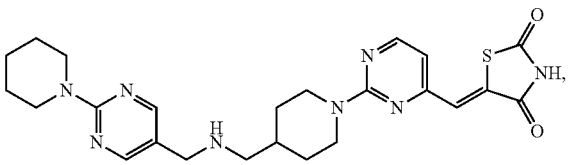

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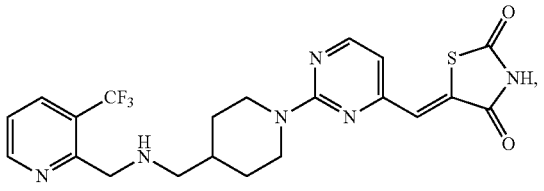

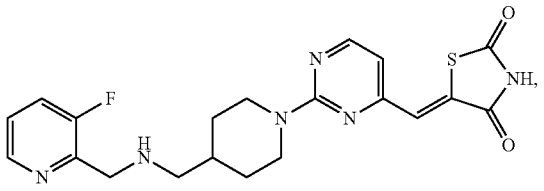

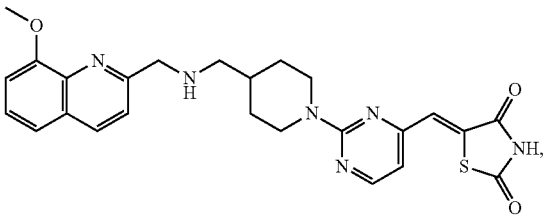

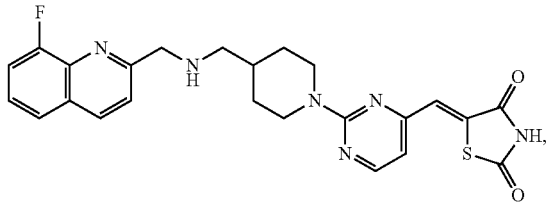

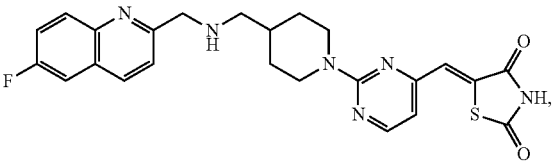

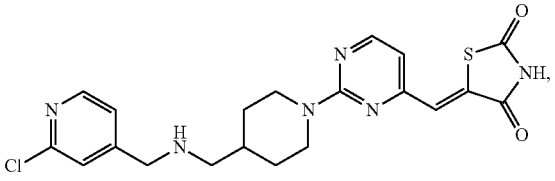

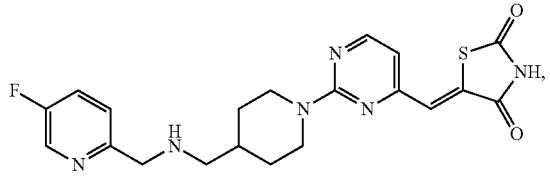

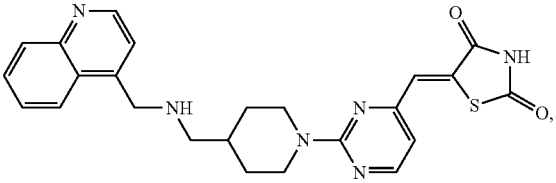

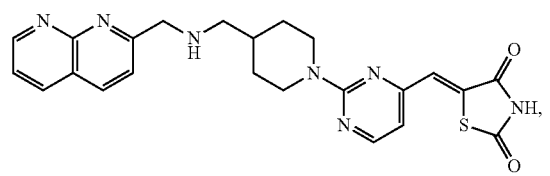

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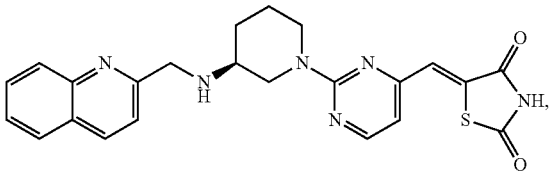

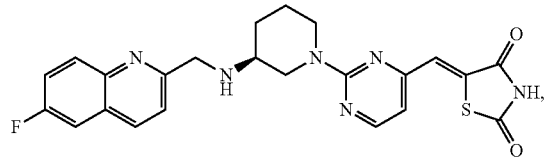

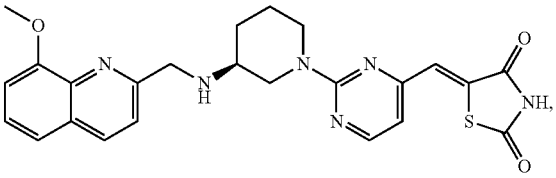

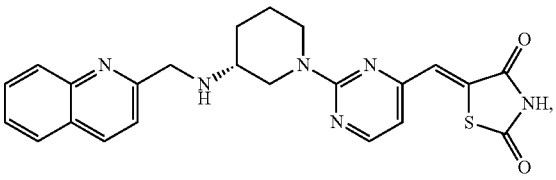

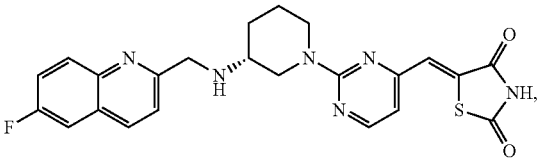

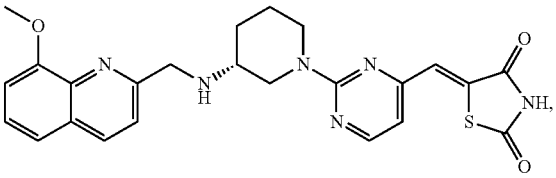

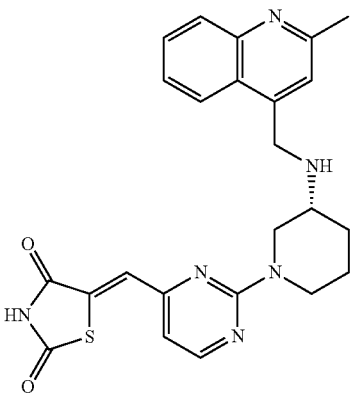

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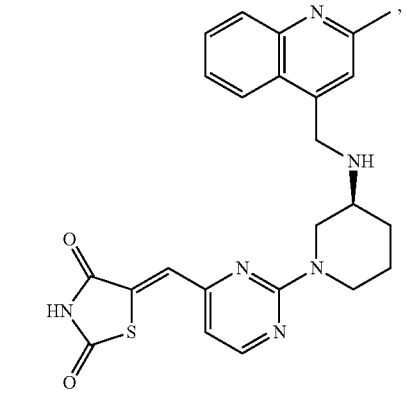

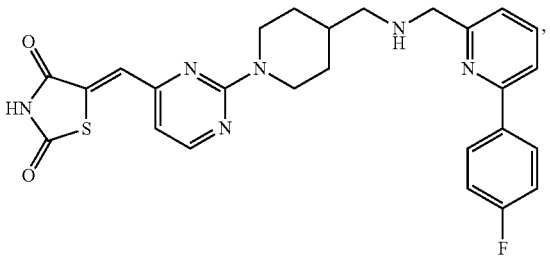

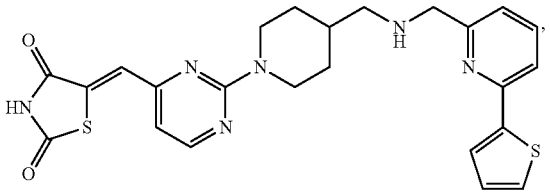

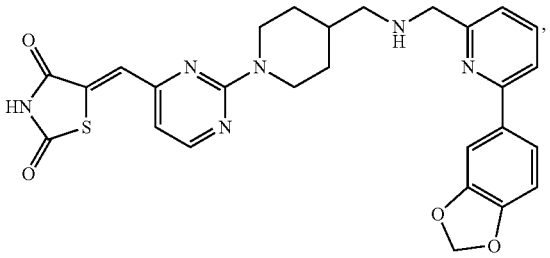

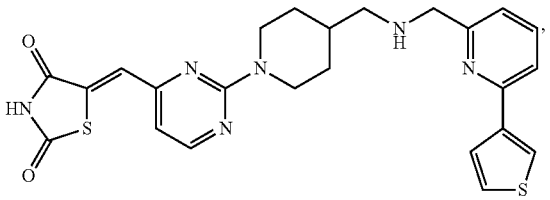

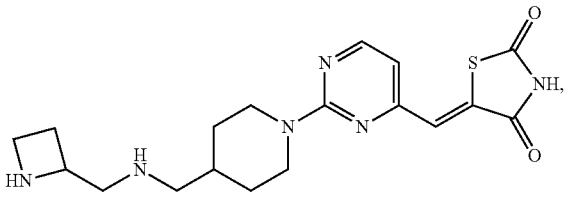

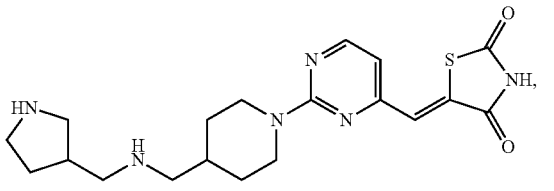

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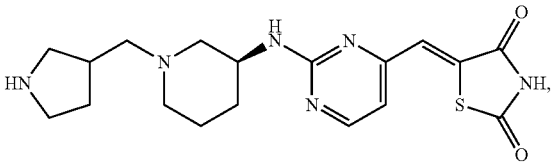

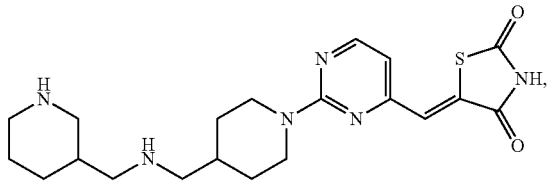

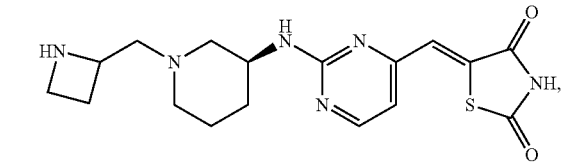

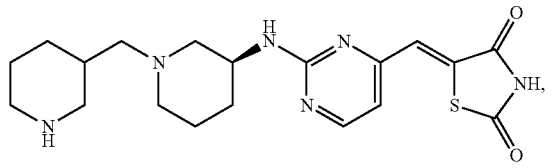

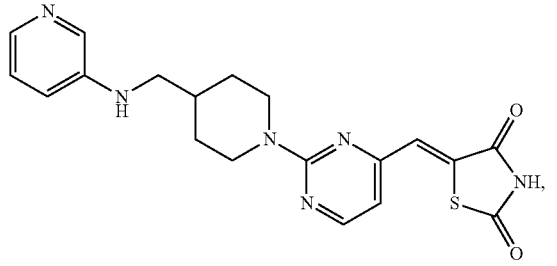

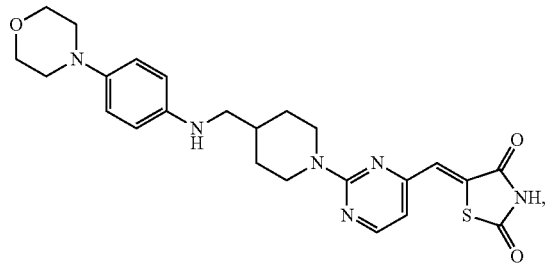

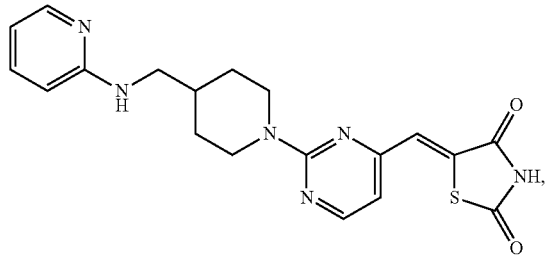

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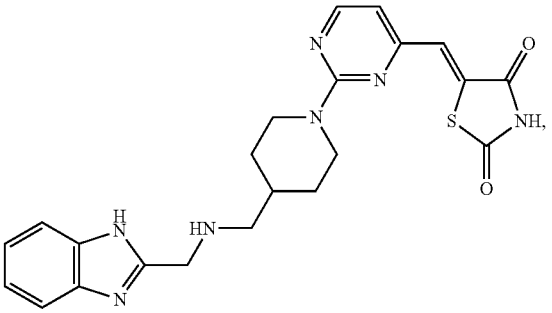

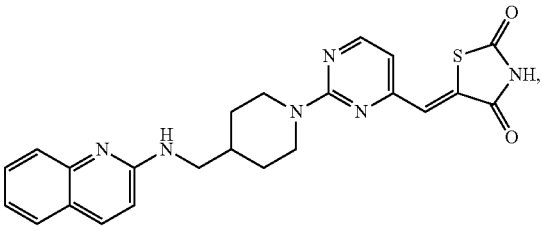

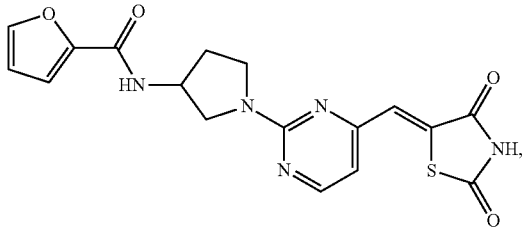

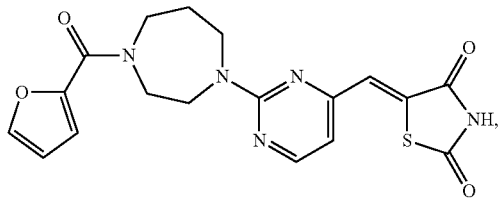

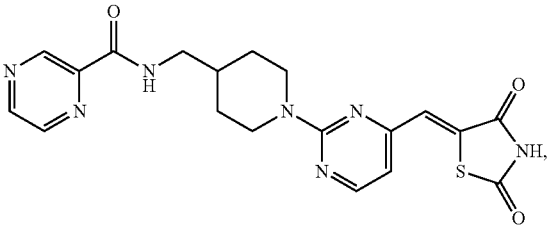

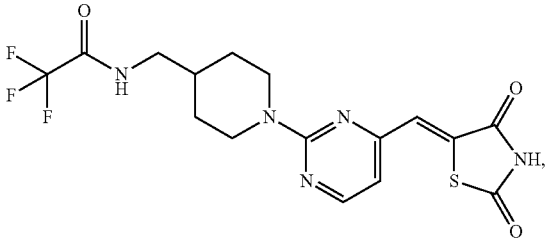

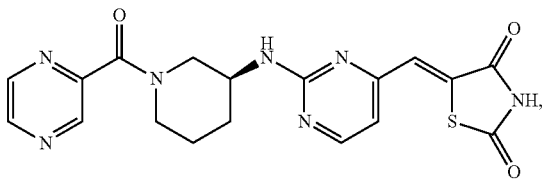

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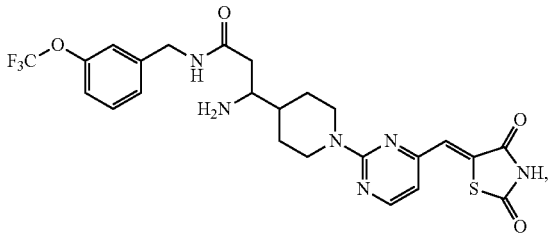

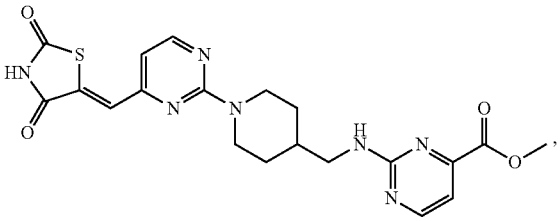

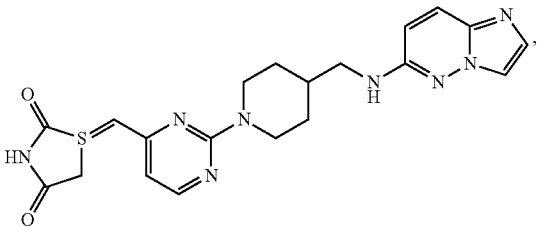

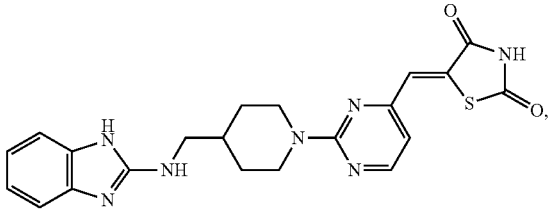

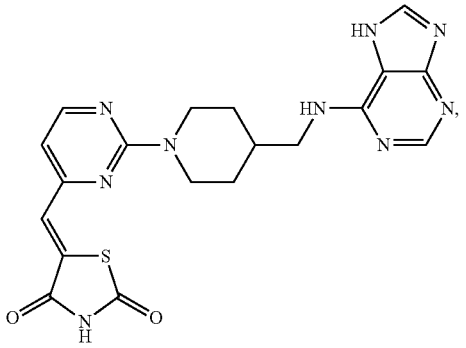

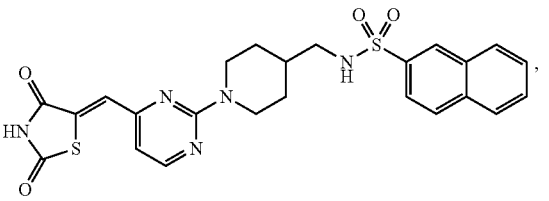

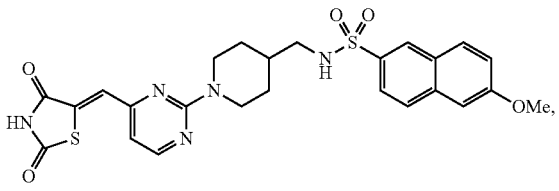

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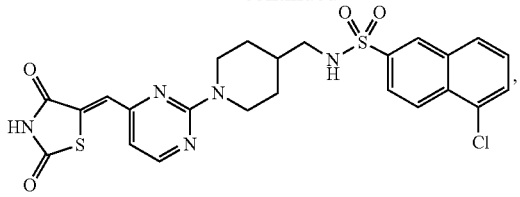
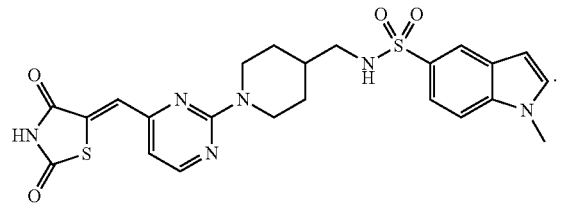
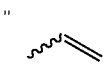


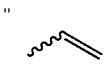
and



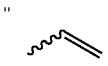
Any one of the aforementioned compounds may exist as the E-geometric isomer, the Z-geometric isomer, or mixtures thereof. For example, in one embodiment,



in the aforementioned structures represents the E-isomer of the particular compound. In another embodiment,



represents the Z-isomer of the particular compound. In yet another embodiment,



represents a mixture of E and Z isomers of the particular compound.

In one embodiment, any one of the aforementioned compounds is an inhibitor of CK1γ1, CK1γ2, or CK1γ3.

In one embodiment, any one of the aforementioned compounds is an inhibitor of CK2.

In one embodiment, any one of the aforementioned compounds is an inhibitor of the Wnt pathway.

In one embodiment, any one of the aforementioned compounds is an inhibitor of the JAK/STAT pathway.

In one embodiment, any one of the aforementioned compounds is an inhibitor of the mTOR pathway.

In one embodiment, any one of the aforementioned compounds is a mediator of Pgp degradation and/or drug efflux.

In one embodiment, any one of the aforementioned compounds is an inhibitor of the TGFβ pathway.

In some embodiments, the compound has an IC_{50} of less than 5000 nM for CK1γ1, CK1γ2, or CK1γ3.

In some embodiments, the compound has an IC_{50} of less than 1000 nM for CK1γ1, CK1γ2, or CK1γ3.

In some embodiments, the compound has an IC_{50} of less than 500 nM for CK1γ1, CK1γ2, or CK1γ3.

In one embodiment, any one of the aforementioned compounds is an inhibitor of CK2.

In one embodiment, the compound has an IC_{50} of less than 5000 nM for CK2.

In one embodiment, the compound has an IC_{50} of less than 1000 nM for CK2.

In one embodiment, the compound has an IC_{50} of less than 500 nM for CK2.

In one embodiment, any on of the aforementioned compounds is an inhibitor of PIM1, PIM2, or PIM3.

In one embodiment, the compound has an IC_{50} of less than 5000 nM for PIM1, PIM2 or PIM3.

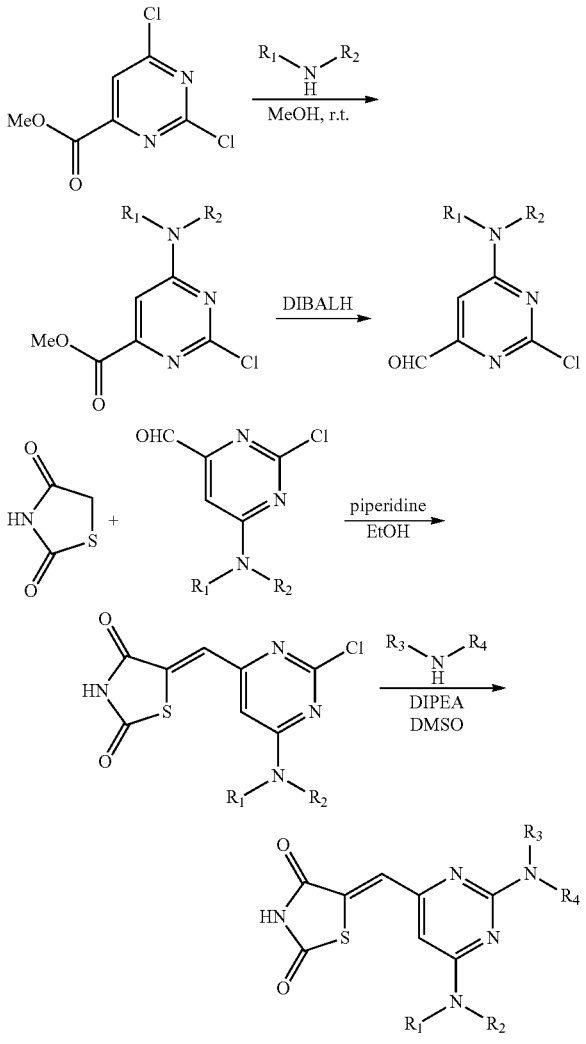
In one embodiment, the compound has an IC_{50} of less than 1000 nM for PIM1, PIM2 or PIM3.

In one embodiment, the compound has an IC_{50} of less than 500 nM for PIM1, PIM2 or PIM3.

General Synthetic Schemes

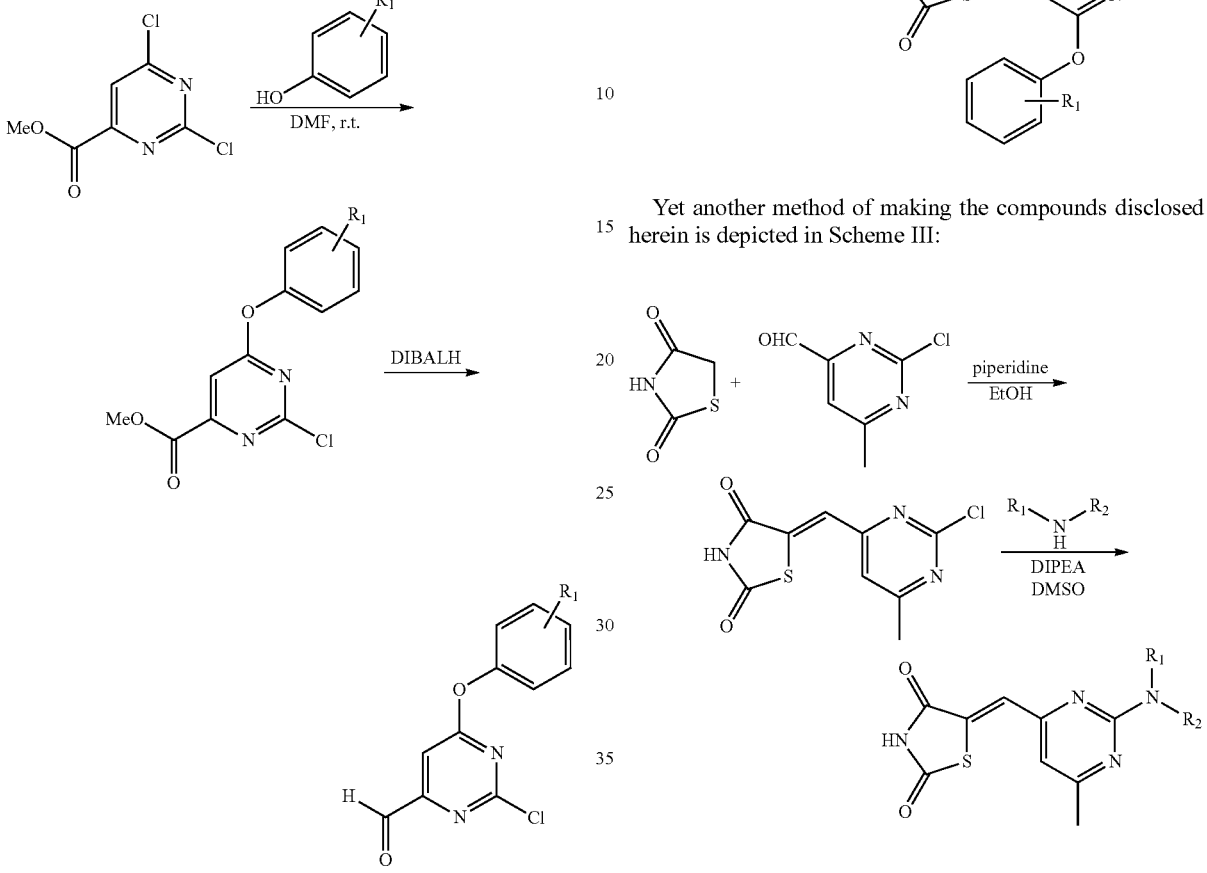
General synthetic schemes that were utilized to prepare compounds disclosed in this application are described below. For example, compounds of the invention may be prepared as shown in Scheme I:

Scheme I.



Alternatively, the compounds of the invention can be made as shown in Scheme II:

Scheme II.



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Yet another method of making the compounds disclosed herein is depicted in Scheme III:

Prophetic Embodiments

Certain compounds of the invention could be made in accordance with the above schemes by reacting an amine (Reactant A) with the hydantoin core (Reactant B). Non-limiting prophetic examples of Reactant A and Reactant B are shown in Table 1 and Table 2, respectively.

TABLE 1

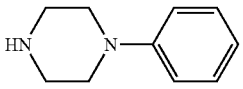
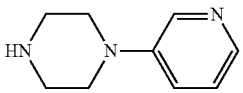
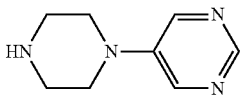
Reactant A Prophetic Examples.	
Reactant A #1	
Structure	
Molecular Weight	162.232
Molecular Formula	$C_{10}H_{14}N_2$
Chemical name	1-phenylpiperazine
Reactant A #2	
Structure	
Molecular Weight	163.22
Molecular Formula	$C_9H_{13}N_3$
Chemical name	1-(pyridin-3-yl)piperazine

TABLE 1-continued

Reactant A Prophetic Examples.

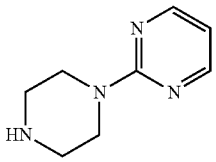
Reactant A #3

Structure



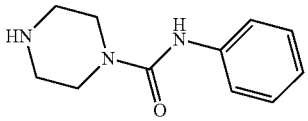
Molecular Weight 164.208
Molecular Formula $C_8H_{12}N_4$
Chemical name 5-(piperazin-1-yl)pyrimidine
Reactant A #4

Structure



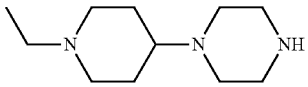
Molecular Weight 164.208
Molecular Formula $C_8H_{12}N_4$
Chemical name 2-(piperazin-1-yl)pyrimidine
Reactant A #5

Structure



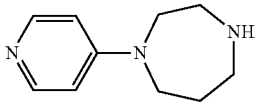
Molecular Weight 205.256
Molecular Formula $C_{11}H_{15}N_3O$
Chemical name N-phenylpiperazine-1-carboxamide
Reactant A #6

Structure



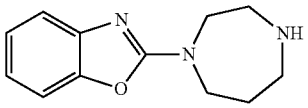
Molecular Weight 197.32
Molecular Formula $C_{11}H_{23}N_3$
Chemical name 1-(1-ethylpiperidin-4-yl)piperazine
Reactant A #7

Structure



Molecular Weight 177.246
Molecular Formula $C_{10}H_{15}N_3$
Chemical name 1-(pyridin-4-yl)-1,4-diazepane
Reactant A #8

Structure



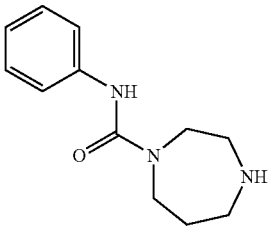
Molecular Weight 217.267
Molecular Formula $C_{12}H_{15}N_3O$
Chemical name 2-(1,4-diazepan-1-yl)benzo[d]oxazole

TABLE 1-continued

Reactant A Prophetic Examples.

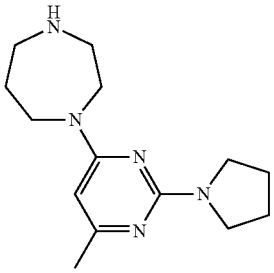
Reactant A #9

Structure



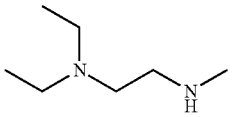
Molecular Weight 219.283
Molecular Formula $C_{12}H_{17}N_3O$
Chemical name N-phenyl-1,4-diazepane-1-carboxamide
Reactant A #10

Structure



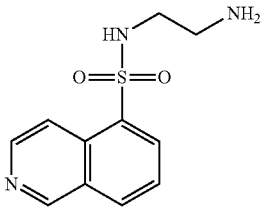
Molecular Weight 261.366
Molecular Formula $C_{14}H_{23}N_5$
Chemical name 1-(6-methyl-2-(pyrrolidin-1-yl)pyrimidin-4-yl)-1,4-diazepane
Reactant A #11

Structure



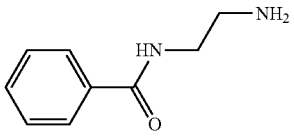
Molecular Weight 130.231
Molecular Formula $C_7H_{18}N_2$
Chemical name N1,N1-diethyl-N2-methylethane-1,2-diamine
Reactant A #12

Structure



Molecular Weight 251.305
Molecular Formula $C_{11}H_{13}N_3O_2S$
Chemical name N-(2-aminoethyl)isoquinoline-5-sulfonamide
Reactant A #13

Structure



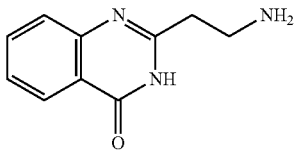
Molecular Weight 164.204
Molecular Formula $C_9H_{12}N_2O$
Chemical name N-(2-aminoethyl)benzamide

TABLE 1-continued

Reactant A Prophetic Examples.

Reactant A #14

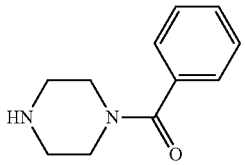
Structure



Molecular Weight 189.214
Molecular Formula $C_{10}H_{11}N_3O$
Chemical name 2-(2-aminoethyl)quinazolin-4(3H)-one

Reactant A #15

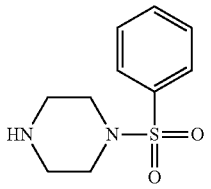
Structure



Molecular Weight 190.242
Molecular Formula $C_{11}H_{14}N_2O$
Chemical name phenyl(piperazin-1-yl)methanone

Reactant A #16

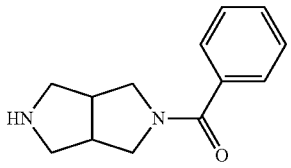
Structure



Molecular Weight 226.295
Molecular Formula $C_{10}H_{14}N_2O_2S$
Chemical name 1-(phenylsulfonyl)piperazine

Reactant A #17

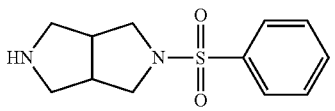
Structure



Molecular Weight 216.279
Molecular Formula $C_{13}H_{16}N_2O$
Chemical name (hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)(phenyl)methanone

Reactant A #18

Structure



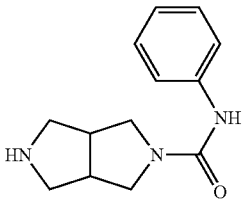
Molecular Weight 252.333
Molecular Formula $C_{12}H_{16}N_2O_2S$
Chemical name 2-(phenylsulfonyl)octahydropyrrolo[3,4-c]pyrrole

TABLE 1-continued

Reactant A Prophetic Examples.

Reactant A #19

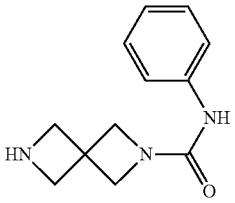
Structure



Molecular Weight 231.294
Molecular Formula $C_{13}H_{17}N_3O$
Chemical name N-phenylhexahydropyrrolo[3,4-c]pyrrole-2(1H)-carboxamide

Reactant A #20

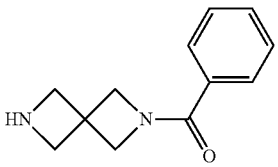
Structure



Molecular Weight 217.267
Molecular Formula $C_{12}H_{15}N_3O$
Chemical name N-phenyl-2,6-diazaspiro[3.3]heptane-2-carboxamide

Reactant A #21

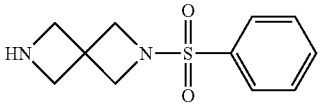
Structure



Molecular Weight 202.252
Molecular Formula $C_{12}H_{14}N_2O$
Chemical name phenyl(2,6-diazaspiro[3.3]heptan-2-yl)methanone

Reactant A #22

Structure



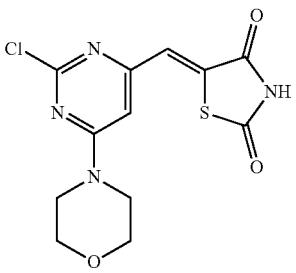
Molecular Weight 238.306
Molecular Formula $C_{11}H_{14}N_2O_2S$
Chemical name 2-(phenylsulfonyl)-2,6-diazaspiro[3.3]heptane

TABLE 2

Reactant B Prophetic Examples.

Reactant B #1

Structure



Molecular Formula $C_{12}H_{11}ClN_4O_3S$

TABLE 2-continued

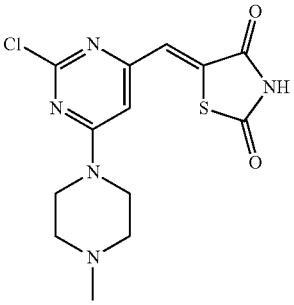
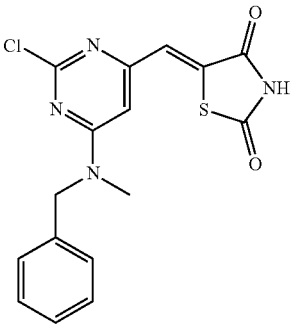
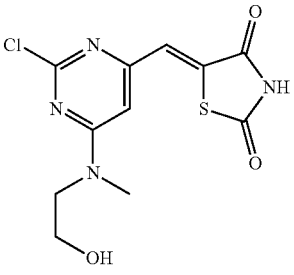
Reactant B Prophetic Examples.	
Molecular Weight	326.759
Chemical name	(Z)-5-((2-chloro-6-morpholinopyrimidin-4-yl)methylene)thiazolidine-2,4-dione
Reactant B #2	
Structure	
Molecular Formula	$C_{13}H_{14}ClN_5O_2S$
Molecular Weight	339.801
Chemical name	(Z)-5-((2-chloro-6-(4-methylpiperazin-1-yl) pyrimidin-4-yl)methylene)thiazolidine-2,4-dione
Reactant B #3	
Structure	
Molecular Formula	$C_{16}H_{13}ClN_4O_2S$
Molecular Weight	360.818
Chemical name	(Z)-5-((6-(benzyl(methyl)amino)-2-chloropyrimidin-4-yl)methylene)thiazolidine-2,4-dione
Reactant B #4	
Structure	
Molecular Formula	$C_{11}H_{11}ClN_4O_3S$
Molecular Weight	314.748
Chemical name	(Z)-5-((2-chloro-6-((2-hydroxyethyl)(methyl)amino)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione

TABLE 2-continued

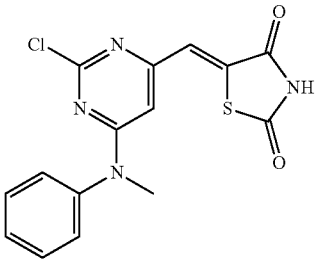
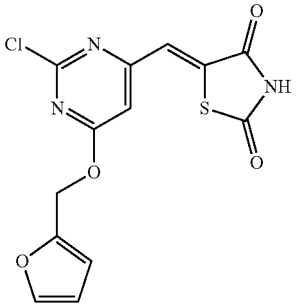
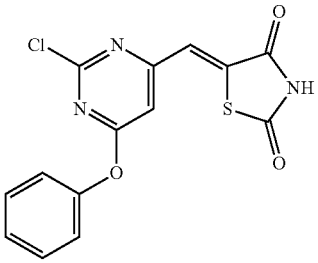
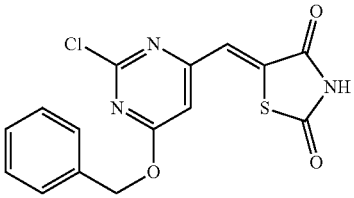
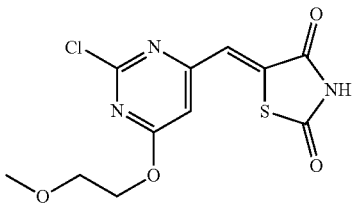
Reactant B Prophetic Examples.	
Reactant B #5	
Structure	
Molecular Formula	$C_{15}H_{11}ClN_4O_2S$
Molecular Weight	346.791
Chemical name	(Z)-5-((2-chloro-6-(methyl(phenyl)amino) pyrimidin-4-yl)methylene)thiazolidine-2,4-dione
Reactant B #6	
Structure	
Molecular Formula	$C_{13}H_8ClN_3O_4S$
Molecular Weight	337.738
Chemical name	(Z)-5-((2-chloro-6-(furan-2-ylmethoxy)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione
Reactant B #7	
Structure	
Molecular Formula	$C_{14}H_8ClN_3O_3S$
Molecular Weight	333.75
Chemical name	(Z)-5-((2-chloro-6-phenoxypyrimidin-4-yl)methylene)thiazolidine-2,4-dione
Reactant B #8	
Structure	
Molecular Formula	$C_{15}H_{10}ClN_3O_3S$
Molecular Weight	347.776
Chemical name	(Z)-5-((6-(benzyloxy)-2-chloropyrimidin-4-yl)methylene)thiazolidine-2,4-dione

TABLE 2-continued

Reactant B Prophetic Examples.

Reactant B #9

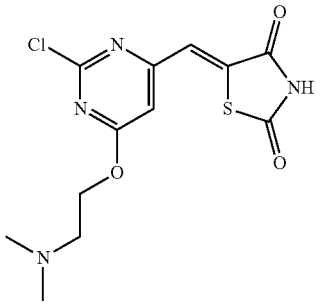
Structure



Molecular Formula	$C_{11}H_{10}ClN_3O_4S$
Molecular Weight	315.733
Chemical name	(Z)-5-((2-chloro-6-(2-methoxyethoxy)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione

Reactant B #10

Structure



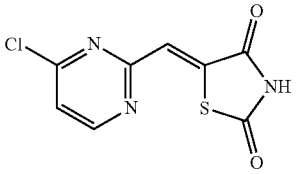
Molecular Formula	$C_{12}H_{13}ClN_4O_3S$
Molecular Weight	328.775
Chemical name	(Z)-5-((2-chloro-6-(2-(dimethylamino)ethoxy) pyrimidin-4-yl)methylene)thiazolidine-2,4-dione

TABLE 2-continued

Reactant B Prophetic Examples.

Reactant B #11

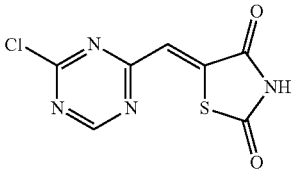
Structure



Molecular Formula	$C_8H_4ClN_3O_2S$
Molecular Weight	241.654
Chemical name	(Z)-5-((2-chloropyrimidin-4-yl)methylene) thiazolidine-2,4-dione

Reactant B #12

Structure



Molecular Formula	$C_7H_3ClN_4O_2S$
Molecular Weight	242.642
Chemical name	(Z)-5-((4-chloro-1,3,5-triazin-2-yl) methylene)thiazolidine-2,4-dione

Additional prophetic embodiments of the invention that may be made in accordance with the above reaction schemes using Reactants A and B are listed in Table 3. The geometric isomers listed in Table 3 are believed to reflect the actual geometry of the prophetic compounds if they were to be made; however, final structural assignments may only be made if the compounds are synthesized and subjected to appropriate 2D NMR experiments. Further, although the compounds are listed as the "Z" geometric isomer, both the E and Z geometric isomers and mixtures thereof are contemplated.

TABLE 3

Additional prophetic embodiments of the invention.

No.	Chemical Name	Formula	Mol. Weight	Reactant A	Reactant B
1	(Z)-5-((6-morpholino-2-(4-phenylpiperazin-1-yl)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione	$C_{22}H_{24}N_6O_3S$	452.529	1	1
2	(Z)-5-((6-morpholino-2-(4-(pyridin-3-yl)piperazin-1-yl)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione	$C_{21}H_{23}N_7O_3S$	453.517	2	1
3	(Z)-5-((6-morpholino-2-(4-(pyrimidin-5-yl)piperazin-1-yl)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione	$C_{20}H_{22}N_8O_3S$	454.505	3	1
4	(Z)-5-((6-morpholino-2-(4-(pyrimidin-2-yl)piperazin-1-yl)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione	$C_{20}H_{22}N_8O_3S$	454.505	4	1
5	(Z)-4-(4-((2,4-dioxothiazolidin-5-ylidene)methyl)-6-morpholinopyrimidin-2-yl)-N-phenylpiperazine-1-carboxamide	$C_{23}H_{25}N_7O_4S$	495.554	5	1
6	(Z)-5-((2-(4-(1-ethylpiperidin-4-yl)piperazin-1-yl)-6-morpholinopyrimidin-4-yl)methylene)thiazolidine-2,4-dione	$C_{23}H_{33}N_7O_3S$	487.618	6	1
7	(Z)-5-((6-morpholino-2-(4-(pyridin-4-yl)-1,4-diazepan-1-yl)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione	$C_{22}H_{25}N_7O_3S$	467.544	7	1
8	(Z)-5-((2-(4-(benzo[d]oxazol-2-yl)-1,4-diazepan-1-yl)-6-morpholinopyrimidin-4-yl)methylene)thiazolidine-2,4-dione	$C_{24}H_{25}N_7O_4S$	507.565	8	1
9	(Z)-4-(4-((2,4-dioxothiazolidin-5-ylidene)methyl)-6-morpholinopyrimidin-2-yl)-N-phenyl-1,4-diazepane-1-carboxamide	$C_{24}H_{27}N_7O_4S$	509.581	9	1

TABLE 3-continued

Additional prophetic embodiments of the invention.

No.	Chemical Name	Formula	Mol. Weight	Reactant A	Reactant B
10	(Z)-5-((2-(4-(6-methyl-2-(pyrrolidin-1-yl)pyrimidin-4-yl)-1,4-diazepan-1-yl)-6-morpholinopyrimidin-4-yl)methylene)thiazolidine-2,4-dione	$C_{26}H_{33}N_9O_3S$	551.664	10	1
11	(Z)-5-((2-((2-(diethylamino)ethyl)(methyl)amino)-6-morpholinopyrimidin-4-yl)methylene)thiazolidine-2,4-dione	$C_{19}H_{28}N_6O_3S$	420.529	11	1
12	(Z)-N-(2-((4-((2,4-dioxothiazolidin-5-ylidene)methyl)-6-morpholinopyrimidin-2-yl)amino)ethyl)isoquinoline-5-sulfonamide	$C_{23}H_{23}N_7O_5S_2$	541.603	12	1
13	(Z)-N-(2-((4-((2,4-dioxothiazolidin-5-ylidene)methyl)-6-morpholinopyrimidin-2-yl)amino)ethyl)benzamide	$C_{21}H_{22}N_6O_4S$	454.502	13	1
14	(Z)-5-((6-morpholino-2-((2-(4-oxo-3,4-dihydroquinazolin-2-yl)ethyl)amino)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione	$C_{22}H_{21}N_7O_4S$	479.512	14	1
15	(Z)-5-((2-(4-benzoylpiperazin-1-yl)-6-morpholinopyrimidin-4-yl)methylene)thiazolidine-2,4-dione	$C_{23}H_{24}N_6O_4S$	480.539	15	1
16	(Z)-5-((6-morpholino-2-(4-(phenylsulfonyl)piperazin-1-yl)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione	$C_{22}H_{24}N_6O_5S_2$	516.593	16	1
17	(Z)-5-((2-(5-benzoylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-6-morpholinopyrimidin-4-yl)methylene)thiazolidine-2,4-dione	$C_{25}H_{26}N_6O_4S$	506.577	17	1
18	(Z)-5-((6-morpholino-2-(5-(phenylsulfonyl)hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione	$C_{24}H_{26}N_6O_5S_2$	542.63	18	1
19	(Z)-5-(4-((2,4-dioxothiazolidin-5-ylidene)methyl)-6-morpholinopyrimidin-2-yl)-N-phenylhexahydropyrrolo[3,4-c]pyrrole-2(1H)-carboxamide	$C_{25}H_{27}N_7O_4S$	521.591	19	1
20	(Z)-6-(4-((2,4-dioxothiazolidin-5-ylidene)methyl)-6-morpholinopyrimidin-2-yl)-N-phenyl-2,6-diazaspiro[3.3]heptane-2-carboxamide	$C_{24}H_{25}N_7O_4S$	507.565	20	1
21	(Z)-5-((2-(6-benzoyl-2,6-diazaspiro[3.3]heptan-2-yl)-6-morpholinopyrimidin-4-yl)methylene)thiazolidine-2,4-dione	$C_{24}H_{24}N_6O_4S$	492.55	21	1
22	(Z)-5-((6-morpholino-2-(6-(phenylsulfonyl)-2,6-diazaspiro[3.3]heptan-2-yl)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione	$C_{23}H_{24}N_6O_5S_2$	528.604	22	1
23	(Z)-5-((6-(4-methylpiperazin-1-yl)-2-(4-phenylpiperazin-1-yl)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione	$C_{23}H_{27}N_7O_2S$	465.571	1	2
24	(Z)-5-((6-(4-methylpiperazin-1-yl)-2-(4-(pyridin-3-yl)piperazin-1-yl)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione	$C_{22}H_{26}N_8O_2S$	466.559	2	2
25	(Z)-5-((6-(4-methylpiperazin-1-yl)-2-(4-(pyrimidin-5-yl)piperazin-1-yl)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione	$C_{21}H_{25}N_9O_2S$	467.547	3	2
26	(Z)-5-((6-(4-methylpiperazin-1-yl)-2-(4-(pyrimidin-2-yl)piperazin-1-yl)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione	$C_{21}H_{25}N_9O_2S$	467.547	4	2
27	(Z)-4-(4-((2,4-dioxothiazolidin-5-ylidene)methyl)-6-(4-methylpiperazin-1-yl)pyrimidin-2-yl)-N-phenylpiperazine-1-carboxamide	$C_{24}H_{28}N_8O_3S$	508.596	5	2
28	(Z)-5-((2-(4-(1-ethylpiperidin-4-yl)piperazin-1-yl)-6-(4-methylpiperazin-1-yl)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione	$C_{24}H_{36}N_8O_2S$	500.66	6	2
29	(Z)-5-((6-(4-methylpiperazin-1-yl)-2-(4-(pyridin-4-yl)-1,4-diazepan-1-yl)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione	$C_{23}H_{28}N_8O_2S$	480.586	7	2
30	(Z)-5-((2-(4-(benzo[d]oxazol-2-yl)-1,4-diazepan-1-yl)-6-(4-methylpiperazin-1-yl)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione	$C_{25}H_{28}N_8O_3S$	520.607	8	2
31	(Z)-4-(4-((2,4-dioxothiazolidin-5-ylidene)methyl)-6-(4-methylpiperazin-1-yl)pyrimidin-2-yl)-N-phenyl-1,4-diazepane-1-carboxamide	$C_{25}H_{30}N_8O_3S$	522.623	9	2
32	(Z)-5-((2-(4-(6-methyl-2-(pyrrolidin-1-yl)pyrimidin-4-yl)-1,4-diazepan-1-yl)-6-(4-methylpiperazin-1-yl)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione	$C_{27}H_{36}N_{10}O_2S$	564.706	10	2
33	(Z)-5-((2-((2-(diethylamino)ethyl)(methyl)amino)-6-(4-methylpiperazin-1-yl)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione	$C_{20}H_{31}N_7O_2S$	433.571	11	2
34	(Z)-N-(2-((4-((2,4-dioxothiazolidin-5-ylidene)methyl)-6-(4-methylpiperazin-1-yl)pyrimidin-2-yl)amino)ethyl)isoquinoline-5-sulfonamide	$C_{24}H_{26}N_8O_4S_2$	554.644	12	2

TABLE 3-continued

Additional prophetic embodiments of the invention.

No.	Chemical Name	Formula	Mol. Weight	Reactant A	Reactant B
35	(Z)-N-(2-((4-((2,4-dioxothiazolidin-5-ylidene)methyl)-6-(4-methylpiperazin-1-yl)pyrimidin-2-yl)amino)ethyl)benzamide	$C_{22}H_{25}N_7O_3S$	467.544	13	2
36	(Z)-5-((6-(4-methylpiperazin-1-yl)-2-((2-(4-oxo-3,4-dihydroquinazolin-2-yl)ethyl)amino)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione	$C_{23}H_{24}N_8O_3S$	492.553	14	2
37	(Z)-5-((2-(4-benzoylpiperazin-1-yl)-6-(4-methylpiperazin-1-yl)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione	$C_{24}H_{27}N_7O_3S$	493.581	15	2
38	(Z)-5-((6-(4-methylpiperazin-1-yl)-2-(4-(phenylsulfonyl)piperazin-1-yl)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione	$C_{23}H_{27}N_7O_4S_2$	529.635	16	2
39	(Z)-5-((2-(5-benzoylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-6-(4-methylpiperazin-1-yl)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione	$C_{26}H_{29}N_7O_3S$	519.619	17	2
40	(Z)-5-((6-(4-methylpiperazin-1-yl)-2-(5-(phenylsulfonyl)hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione	$C_{25}H_{29}N_7O_4S_2$	555.672	18	2
41	(Z)-5-(4-((2,4-dioxothiazolidin-5-ylidene)methyl)-6-(4-methylpiperazin-1-yl)pyrimidin-2-yl)-N-phenylhexahydropyrrolo[3,4-c]pyrrole-2(1H)-carboxamide	$C_{26}H_{30}N_8O_3S$	534.633	19	2
42	(Z)-6-(4-((2,4-dioxothiazolidin-5-ylidene)methyl)-6-(4-methylpiperazin-1-yl)pyrimidin-2-yl)-N-phenyl-2,6-diazaspiro[3.3]heptane-2-carboxamide	$C_{25}H_{28}N_8O_3S$	520.607	20	2
43	(Z)-5-((2-(6-benzoyl-2,6-diazaspiro[3.3]heptan-2-yl)-6-(4-methylpiperazin-1-yl)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione	$C_{25}H_{27}N_7O_3S$	505.592	21	2
44	(Z)-5-((6-(4-methylpiperazin-1-yl)-2-(6-(phenylsulfonyl)-2,6-diazaspiro[3.3]heptan-2-yl)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione	$C_{24}H_{27}N_7O_4S_2$	541.646	22	2
45	(Z)-5-((6-(benzyl(methyl)amino)-2-(4-phenylpiperazin-1-yl)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione	$C_{26}H_{26}N_6O_2S$	486.589	1	3
46	(Z)-5-((6-(benzyl(methyl)amino)-2-(4-(pyridin-3-yl)piperazin-1-yl)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione	$C_{25}H_{25}N_7O_2S$	487.577	2	3
47	(Z)-5-((6-(benzyl(methyl)amino)-2-(4-(pyrimidin-5-yl)piperazin-1-yl)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione	$C_{24}H_{24}N_8O_2S$	488.565	3	3
48	(Z)-5-((6-(benzyl(methyl)amino)-2-(4-(pyrimidin-2-yl)piperazin-1-yl)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione	$C_{24}H_{24}N_8O_2S$	488.565	4	3
49	(Z)-4-(4-(benzyl(methyl)amino)-6-((2,4-dioxothiazolidin-5-ylidene)methyl)pyrimidin-2-yl)-N-phenylpiperazine-1-carboxamide	$C_{27}H_{27}N_7O_3S$	529.613	5	3
50	(Z)-5-((6-(benzyl(methyl)amino)-2-(4-(1-ethylpiperidin-4-yl)piperazin-1-yl)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione	$C_{27}H_{35}N_7O_2S$	521.678	6	3
51	(Z)-5-((6-(benzyl(methyl)amino)-2-(4-(pyridin-4-yl)-1,4-diazepan-1-yl)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione	$C_{26}H_{27}N_7O_2$	501.603	7	3
52	(Z)-5-((2-(4-(benzo[d]oxazol-2-yl)-1,4-diazepan-1-yl)-6-(benzyl(methyl)amino)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione	$C_{28}H_{27}N_7O_3S$	541.624	8	3
53	(Z)-4-(4-(benzyl(methyl)amino)-6-((2,4-dioxothiazolidin-5-ylidene)methyl)pyrimidin-2-yl)-N-phenyl-1,4-diazepane-1-carboxamide	$C_{28}H_{29}N_7O_3S$	543.64	9	3
54	(Z)-5-((6-(benzyl(methyl)amino)-2-(4-(6-methyl-2-(pyrrolidin-1-yl)pyrimidin-4-yl)-1,4-diazepan-1-yl)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione	$C_{30}H_{35}N_9O_2S$	585.723	10	3
55	(Z)-5-((6-(benzyl(methyl)amino)-2-((2-(diethylamino)ethyl)(methyl)amino)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione	$C_{23}H_{30}N_6O_2S$	454.588	11	3
56	(Z)-N-(2-((4-(benzyl(methyl)amino)-6-((2,4-dioxothiazolidin-5-ylidene)methyl)pyrimidin-2-yl)amino)ethyl)isoquinoline-5-sulfonamide	$C_{27}H_{25}N_7O_4S_2$	575.662	12	3
57	(Z)-N-(2-((4-(benzyl(methyl)amino)-6-((2,4-dioxothiazolidin-5-ylidene)methyl)pyrimidin-2-yl)amino)ethyl)benzamide	$C_{25}H_{24}N_6O_3S$	488.561	13	3
58	(Z)-5-((6-(benzyl(methyl)amino)-2-((2-(4-oxo-3,4-dihydroquinazolin-2-yl)ethyl)amino)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione	$C_{26}H_{23}N_7O_3S$	513.571	14	3

TABLE 3-continued

Additional prophetic embodiments of the invention.

No.	Chemical Name	Formula	Mol. Weight	Reactant A	Reactant B
59	(Z)-5-((2-(4-benzoylpiperazin-1-yl)-6-(benzyl(methyl)amino)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione	$C_{27}H_{26}N_6O_3S$	514.599	15	3
60	(Z)-5-((6-(benzyl(methyl)amino)-2-(4-(phenylsulfonyl)piperazin-1-yl)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione	$C_{26}H_{26}N_6O_4S_2$	550.652	16	3
61	(Z)-5-((2-(5-benzoylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-6-(benzyl(methyl)amino)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione	$C_{29}H_{28}N_6O_3S$	540.636	17	3
62	(Z)-5-((6-(benzyl(methyl)amino)-2-(5-(phenylsulfonyl)hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione	$C_{28}H_{28}N_6O_4S_2$	576.69	18	3
63	(Z)-5-(4-(benzyl(methyl)amino)-6-((2,4-dioxothiazolidin-5-ylidene)methyl)pyrimidin-2-yl)-N-phenylhexahydropyrrolo[3,4-c]pyrrole-2(1H)-carboxamide	$C_{29}H_{29}N_7O_3S$	555.651	19	3
64	(Z)-6-(4-(benzyl(methyl)amino)-6-((2,4-dioxothiazolidin-5-ylidene)methyl)pyrimidin-2-yl)-N-phenyl-2,6-diazaspiro[3.3]heptane-2-carboxamide	$C_{28}H_{27}N_7O_3S$	541.624	20	3
65	(Z)-5-((2-(6-benzoyl-2,6-diazaspiro[3.3]heptan-2-yl)-6-(benzyl(methyl)amino)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione	$C_{28}H_{26}N_6O_3S$	526.609	21	3
66	(Z)-5-((6-(benzyl(methyl)amino)-2-(6-(phenylsulfonyl)-2,6-diazaspiro[3.3]heptan-2-yl)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione	$C_{27}H_{26}N_6O_4S_2$	562.663	22	3
67	(Z)-5-((6-((2-hydroxyethyl)(methyl)amino)-2-(4-phenylpiperazin-1-yl)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione	$C_{21}H_{24}N_6O_3S$	440.519	1	4
68	(Z)-5-((6-((2-hydroxyethyl)(methyl)amino)-2-(4-(pyridin-3-yl)piperazin-1-yl)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione	$C_{20}H_{23}N_7O_3S$	441.507	2	4
69	(Z)-5-((6-((2-hydroxyethyl)(methyl)amino)-2-(4-(pyrimidin-5-yl)piperazin-1-yl)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione	$C_{19}H_{22}N_8O_3S$	442.495	3	4
70	(Z)-5-((6-((2-hydroxyethyl)(methyl)amino)-2-(4-(pyrimidin-2-yl)piperazin-1-yl)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione	$C_{19}H_{22}N_8O_3S$	442.495	4	4
71	(Z)-4-(4-((2,4-dioxothiazolidin-5-ylidene)methyl)-6-((2-hydroxyethyl)(methyl)amino)pyrimidin-2-yl)-N-phenylpiperazine-1-carboxamide	$C_{22}H_{25}N_7O_4S$	483.543	5	4
72	(Z)-5-((2-(4-(1-ethylpiperidin-4-yl)piperazin-1-yl)-6-((2-hydroxyethyl)(methyl)amino)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione	$C_{22}H_{33}N_7O_3S$	475.608	6	4
73	(Z)-5-((6-((2-hydroxyethyl)(methyl)amino)-2-(4-(pyridin-4-yl)-1,4-diazepan-1-yl)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione	$C_{21}H_{25}N_7O_3S$	455.533	7	4
74	(Z)-5-((2-(4-(benzo[d]oxazol-2-yl)-1,4-diazepan-1-yl)-6-((2-hydroxyethyl)(methyl)amino)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione	$C_{23}H_{25}N_7O_4S$	495.554	8	4
75	(Z)-4-(4-((2,4-dioxothiazolidin-5-ylidene)methyl)-6-((2-hydroxyethyl)(methyl)amino)pyrimidin-2-yl)-N-phenyl-1,4-diazepane-1-carboxamide	$C_{23}H_{27}N_7O_4S$	497.57	9	4
76	(Z)-5-((6-((2-hydroxyethyl)(methyl)amino)-2-(4-(6-methyl-2-(pyrrolidin-1-yl)pyrimidin-4-yl)-1,4-diazepan-1-yl)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione	$C_{25}H_{33}N_9O_3S$	539.653	10	4
77	(Z)-5-((2-((2-(diethylamino)ethyl)(methyl)amino)-6-((2-hydroxyethyl)(methyl)amino)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione	$C_{18}H_{28}N_6O_3S$	408.518	11	4
78	(Z)-N-(2-((4-((2,4-dioxothiazolidin-5-ylidene)methyl)-6-((2-hydroxyethyl)(methyl)amino)pyrimidin-2-yl)amino)ethyl)isoquinoline-5-sulfonamide	$C_{22}H_{23}N_7O_5S_2$	529.592	12	4
79	(Z)-N-(2-((4-((2,4-dioxothiazolidin-5-ylidene)methyl)-6-((2-hydroxyethyl)(methyl)amino)pyrimidin-2-yl)amino)ethyl)benzamide	$C_{20}H_{22}N_6O_4S$	442.491	13	4
80	(Z)-5-((6-((2-hydroxyethyl)(methyl)amino)-2-((2-(4-oxo-3,4-dihydroquinazolin-2-yl)ethyl)amino)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione	$C_{21}H_{21}N_7O_4S$	467.501	14	4
81	(Z)-5-((2-(4-benzoylpiperazin-1-yl)-6-((2-hydroxyethyl)(methyl)amino)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione	$C_{22}H_{24}N_6O_4S$	468.529	15	4

TABLE 3-continued

Additional prophetic embodiments of the invention.

No.	Chemical Name	Formula	Mol. Weight	Reactant A	Reactant B
82	(Z)-5-((6-((2-hydroxyethyl)(methyl)amino)-2-(4-(phenylsulfonyl)piperazin-1-yl)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione	$C_{21}H_{24}N_6O_5S_2$	504.582	16	4
83	(Z)-5-((2-(5-benzoylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-6-((2-hydroxyethyl)(methyl)amino)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione	$C_{24}H_{26}N_6O_4S$	494.566	17	4
84	(Z)-5-((6-((2-hydroxyethyl)(methyl)amino)-2-(5-(phenylsulfonyl)hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione	$C_{23}H_{26}N_6O_5S_2$	530.62	18	4
85	(Z)-5-(4-((2,4-dioxothiazolidin-5-ylidene)methyl)-6-((2-hydroxyethyl)(methyl)amino)pyrimidin-2-yl)-N-phenylhexahydropyrrolo[3,4-c]pyrrole-2(1H)-carboxamide	$C_{24}H_{27}N_7O_4S$	509.581	19	4
86	(Z)-6-(4-((2,4-dioxothiazolidin-5-ylidene)methyl)-6-((2-hydroxyethyl)(methyl)amino)pyrimidin-2-yl)-N-phenyl-2,6-diazaspiro[3.3]heptane-2-carboxamide	$C_{23}H_{25}N_7O_4S$	495.554	20	4
87	(Z)-5-((2-(6-benzoyl-2,6-diazaspiro[3.3]heptan-2-yl)-6-((2-hydroxyethyl)(methyl)amino)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione	$C_{23}H_{24}N_6O_4S$	480.539	21	4
88	(Z)-5-((6-((2-hydroxyethyl)(methyl)amino)-2-(6-(phenylsulfonyl)-2,6-diazaspiro[3.3]heptan-2-yl)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione	$C_{22}H_{24}N_6O_5S_2$	516.593	22	4
89	(Z)-5-((6-(methyl(phenyl)amino)-2-(4-phenylpiperazin-1-yl)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione	$C_{25}H_{24}N_6O_2S$	472.562	1	5
90	(Z)-5-((6-(methyl(phenyl)amino)-2-(4-(pyridin-3-yl)piperazin-1-yl)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione	$C_{24}H_{23}N_7O_2S$	473.55	2	5
91	(Z)-5-((6-(methyl(phenyl)amino)-2-(4-(pyrimidin-5-yl)piperazin-1-yl)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione	$C_{23}H_{22}N_8O_2S$	474.538	3	5
92	(Z)-5-((6-(methyl(phenyl)amino)-2-(4-(pyrimidin-2-yl)piperazin-1-yl)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione	$C_{23}H_{22}N_8O_2S$	474.538	4	5
93	(Z)-4-(4-((2,4-dioxothiazolidin-5-ylidene)methyl)-6-(methyl(phenyl)amino)pyrimidin-2-yl)-N-phenylpiperazine-1-carboxamide	$C_{26}H_{25}N_7O_3S$	515.587	5	5
94	(Z)-5-((2-(4-(1-ethylpiperidin-4-yl)piperazin-1-yl)-6-(methyl(phenyl)amino)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione	$C_{26}H_{33}N_7O_2S$	507.651	6	5
95	(Z)-5-((6-(methyl(phenyl)amino)-2-(4-(pyridin-4-yl)-1,4-diazepan-1-yl)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione	$C_{25}H_{25}N_7O_2S$	487.577	7	5
96	(Z)-5-((2-(4-(benzo[d]oxazol-2-yl)-1,4-diazepan-1-yl)-6-(methyl(phenyl)amino)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione	$C_{27}H_{25}N_7O_3S$	527.598	8	5
97	(Z)-4-(4-((2,4-dioxothiazolidin-5-ylidene)methyl)-6-(methyl(phenyl)amino)pyrimidin-2-yl)-N-phenyl-1,4-diazepane-1-carboxamide	$C_{27}H_{27}N_7O_3S$	529.613	9	5
98	(Z)-5-((6-(methyl(phenyl)amino)-2-(4-(6-methyl-2-(pyrrolidin-1-yl)pyrimidin-4-yl)-1,4-diazepan-1-yl)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione	$C_{29}H_{33}N_9O_2S$	571.696	10	5
99	(Z)-5-((2-((2-(diethylamino)ethyl)(methyl)amino)-6-(methyl(phenyl)amino)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione	$C_{22}H_{28}N_6O_2S$	440.562	11	5
100	(Z)-N-(2-((4-((2,4-dioxothiazolidin-5-ylidene)methyl)-6-(methyl(phenyl)amino)pyrimidin-2-yl)amino)ethyl)isoquinoline-5-sulfonamide	$C_{26}H_{23}N_7O_4S_2$	561.635	12	5
101	(Z)-N-(2-((4-((2,4-dioxothiazolidin-5-ylidene)methyl)-6-(methyl(phenyl)amino)pyrimidin-2-yl)amino)ethyl)benzamide	$C_{24}H_{22}N_6O_3S$	474.535	13	5
102	(Z)-5-((6-(methyl(phenyl)amino)-2-((2-(4-oxo-3,4-dihydroquinazolin-2-yl)ethyl)amino)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione	$C_{25}H_{21}N_7O_3S$	499.544	14	5
103	(Z)-5-((2-(4-benzoylpiperazin-1-yl)-6-(methyl(phenyl)amino)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione	$C_{26}H_{24}N_6O_3S$	500.572	15	5
104	(Z)-5-((6-(methyl(phenyl)amino)-2-(4-(phenylsulfonyl)piperazin-1-yl)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione	$C_{25}H_{24}N_6O_4S_2$	536.626	16	5
105	(Z)-5-((2-(5-benzoylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-6-(methyl(phenyl)amino)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione	$C_{28}H_{26}N_6O_3S$	526.609	17	5

TABLE 3-continued

Additional prophetic embodiments of the invention.

No.	Chemical Name	Formula	Mol. Weight	Reactant A	Reactant B
106	(Z)-5-((6-(methyl(phenyl)amino)-2-(5-(phenylsulfonyl)hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione	$C_{27}H_{26}N_6O_4S_2$	562.663	18	5
107	(Z)-5-(4-((2,4-dioxothiazolidin-5-ylidene)methyl)-6-(methyl(phenyl)amino)pyrimidin-2-yl)-N-phenylhexahydropyrrolo[3,4-c]pyrrole-2 (1H)-carboxamide	$C_{28}H_{27}N_7O_3S$	541.624	19	5
108	(Z)-6-(4-((2,4-dioxothiazolidin-5-ylidene)methyl)-6-(methyl(phenyl)amino)pyrimidin-2-yl)-N-phenyl-2,6-diazaspiro[3.3]heptane-2-carboxamide	$C_{27}H_{25}N_7O_3S$	527.598	20	5
109	(Z)-5-((2-(6-benzoyl-2,6-diazaspiro[3.3]heptan-2-yl)-6-(methyl(phenyl)amino)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione	$C_{27}H_{24}N_6O_3S$	512.583	21	5
110	(Z)-5-((6-(methyl(phenyl)amino)-2-(6-(phenylsulfonyl)-2,6-diazaspiro[3.3]heptan-2-yl)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione	$C_{26}H_{24}N_6O_4S_2$	548.637	22	5
111	(Z)-5-((6-(furan-2-ylmethoxy)-2-(4-phenylpiperazin-1-yl)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione	$C_{23}H_{21}N_5O_4S$	463.509	1	6
112	(Z)-5-((6-(furan-2-ylmethoxy)-2-(4-(pyridin-3-yl)piperazin-1-yl)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione	$C_{22}H_{20}N_6O_4S$	464.497	2	6
113	(Z)-5-((6-(furan-2-ylmethoxy)-2-(4-(pyrimidin-5-yl)piperazin-1-yl)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione	$C_{21}H_{19}N_7O_4S$	465.485	3	6
114	(Z)-5-((6-(furan-2-ylmethoxy)-2-(4-(pyrimidin-2-yl)piperazin-1-yl)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione	$C_{21}H_{19}N_7O_4S$	465.485	4	6
115	(Z)-4-(4-((2,4-dioxothiazolidin-5-ylidene)methyl)-6-(furan-2-ylmethoxy)pyrimidin-2-yl)-N-phenylpiperazine-1-carboxamide	$C_{24}H_{22}N_6O_5S$	506.534	5	6
116	(Z)-5-((2-(4-(1-ethylpiperidin-4-yl)piperazin-1-yl)-6-(furan-2-ylmethoxy)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione	$C_{24}H_{30}N_6O_4S$	498.598	6	6
117	(Z)-5-((6-(furan-2-ylmethoxy)-2-(4-(pyridin-4-yl)-1,4-diazepan-1-yl)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione	$C_{23}H_{22}N_6O_4S$	478.524	7	6
118	(Z)-5-((2-(4-(benzo[d]oxazol-2-yl)-1,4-diazepan-1-yl)-6-(furan-2-ylmethoxy)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione	$C_{25}H_{22}N_6O_5S$	518.544	8	6
119	(Z)-4-(4-((2,4-dioxothiazolidin-5-ylidene)methyl)-6-(furan-2-ylmethoxy)pyrimidin-2-yl)-N-phenyl-1,4-diazepane-1-carboxamide	$C_{25}H_{24}N_6O_5S$	520.56	9	6
120	(Z)-5-((6-(furan-2-ylmethoxy)-2-(4-(6-methyl-2-(pyrrolidin-1-yl)pyrimidin-4-yl)-1,4-diazepan-1-yl)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione	$C_{27}H_{30}N_8O_4S$	562.643	10	6
121	(Z)-5-((2-((2-(diethylamino)ethyl)(methyl)amino)-6-(furan-2-ylmethoxy)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione	$C_{20}H_{25}N_5O_4S$	431.509	11	6
122	(Z)-N-(2-((4-((2,4-dioxothiazolidin-5-ylidene)methyl)-6-(furan-2-ylmethoxy)pyrimidin-2-yl)amino)ethyl)isoquinoline-5-sulfonamide	$C_{24}H_{20}N_6O_6S_2$	552.582	12	6
123	(Z)-N-(2-((4-((2,4-dioxothiazolidin-5-ylidene)methyl)-6-(furan-2-ylmethoxy)pyrimidin-2-yl)amino)ethyl)benzamide	$C_{22}H_{19}N_5O_5S$	465.482	13	6
124	(Z)-5-((6-(furan-2-ylmethoxy)-2-((2-(4-oxo-3,4-dihydroquinazolin-2-yl)ethyl)amino)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione	$C_{23}H_{18}N_6O_5S$	490.491	14	6
125	(Z)-5-((2-(4-benzoylpiperazin-1-yl)-6-(furan-2-ylmethoxy)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione	$C_{24}H_{21}N_5O_5S$	491.519	15	6
126	(Z)-5-((6-(furan-2-ylmethoxy)-2-(4-(phenylsulfonyl)piperazin-1-yl)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione	$C_{23}H_{21}N_5O_6S_2$	527.573	16	6
127	(Z)-5-((2-(5-benzoylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-6-(furan-2-ylmethoxy)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione	$C_{26}H_{23}N_5O_5S$	517.556	17	6
128	(Z)-5-((6-(furan-2-ylmethoxy)-2-(5-(phenylsulfonyl)hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione	$C_{25}H_{23}N_5O_6S_2$	553.61	18	6
129	(Z)-5-(4-((2,4-dioxothiazolidin-5-ylidene)methyl)-6-(furan-2-ylmethoxy)pyrimidin-2-yl)-N-phenylhexahydropyrrolo[3,4-c]pyrrole-2(1H)-carboxamide	$C_{26}H_{24}N_6O_5S$	532.571	19	6

TABLE 3-continued

Additional prophetic embodiments of the invention.

No.	Chemical Name	Formula	Mol. Weight	Reactant A	Reactant B
130	(Z)-6-(4-((2,4-dioxothiazolidin-5-ylidene)methyl)-6-(furan-2-ylmethoxy)pyrimidin-2-yl)-N-phenyl-2,6-diazaspiro[3.3]heptane-2-carboxamide	$C_{25}H_{22}N_6O_5S$	518.544	20	6
131	(Z)-5-((2-(6-benzoyl-2,6-diazaspiro[3.3]heptan-2-yl)-6-(furan-2-ylmethoxy)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione	$C_{25}H_{21}N_5O_5S$	503.53	21	6
132	(Z)-5-((6-(furan-2-ylmethoxy)-2-(6-(phenylsulfonyl)-2,6-diazaspiro[3.3]heptan-2-yl)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione	$C_{24}H_{21}N_5O_6S_2$	539.583	22	6
133	(Z)-5-((6-phenoxy-2-(4-phenylpiperazin-1-yl)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione	$C_{24}H_{21}N_5O_3S$	459.52	1	7
134	(Z)-5-((6-phenoxy-2-(4-(pyridin-3-yl)piperazin-1-yl)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione	$C_{23}H_{20}N_6O_3S$	460.508	2	7
135	(Z)-5-((6-phenoxy-2-(4-(pyrimidin-5-yl)piperazin-1-yl)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione	$C_{22}H_{19}N_7O_3S$	461.496	3	7
136	(Z)-5-((6-phenoxy-2-(4-(pyrimidin-2-yl)piperazin-1-yl)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione	$C_{22}H_{19}N_7O_3S$	461.496	4	7
137	(Z)-4-(4-((2,4-dioxothiazolidin-5-ylidene)methyl)-6-phenoxypyrimidin-2-yl)-N-phenylpiperazine-1-carboxamide	$C_{25}H_{22}N_6O_4S$	502.545	5	7
138	(Z)-5-((2-(4-(1-ethylpiperidin-4-yl)piperazin-1-yl)-6-phenoxypyrimidin-4-yl)methylene)thiazolidine-2,4-dione	$C_{25}H_{30}N_6O_3S$	494.609	6	7
139	(Z)-5-((6-phenoxy-2-(4-(pyridin-4-yl)-1,4-diazepan-1-yl)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione	$C_{24}H_{22}N_6O_3S$	474.535	7	7
140	(Z)-5-((2-(4-(benzo[d]oxazol-2-yl)-1,4-diazepan-1-yl)-6-phenoxypyrimidin-4-yl)methylene)thiazolidine-2,4-dione	$C_{26}H_{22}N_6O_4S$	514.556	8	7
141	(Z)-4-(4-((2,4-dioxothiazolidin-5-ylidene)methyl)-6-phenoxypyrimidin-2-yl)-N-phenyl-1,4-diazepane-1-carboxamide	$C_{26}H_{24}N_6O_4S$	516.572	9	7
142	(Z)-5-((2-(4-(6-methyl-2-(pyrrolidin-1-yl)pyrimidin-4-yl)-1,4-diazepan-1-yl)-6-phenoxypyrimidin-4-yl)methylene)thiazolidine-2,4-dione	$C_{28}H_{30}N_8O_3S$	558.655	10	7
143	(Z)-5-((2-((2-(diethylamino)ethyl)(methyl)amino)-6-phenoxypyrimidin-4-yl)methylene)thiazolidine-2,4-dione	$C_{21}H_{25}N_5O_3S$	427.52	11	7
144	(Z)-N-(2-((4-((2,4-dioxothiazolidin-5-ylidene)methyl)-6-phenoxypyrimidin-2-yl)amino)ethyl)isoquinoline-5-sulfonamide	$C_{25}H_{20}N_6O_5S_2$	548.594	12	7
145	(Z)-N-(2-((4-((2,4-dioxothiazolidin-5-ylidene)methyl)-6-phenoxypyrimidin-2-yl)amino)ethyl)benzamide	$C_{23}H_{19}N_5O_4S$	461.493	13	7
146	(Z)-5-((2-((2-(4-oxo-3,4-dihydroquinazolin-2-yl)ethyl)amino)-6-phenoxypyrimidin-4-yl)methylene)thiazolidine-2,4-dione	$C_{24}H_{18}N_6O_4S$	486.503	14	7
147	(Z)-5-((2-(4-benzoylpiperazin-1-yl)-6-phenoxypyrimidin-4-yl)methylene)thiazolidine-2,4-dione	$C_{25}H_{21}N_5O_4S$	487.53	15	7
148	(Z)-5-((6-phenoxy-2-(4-(phenylsulfonyl)piperazin-1-yl)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione	$C_{24}H_{21}N_5O_5S_2$	523.584	16	7
149	(Z)-5-((2-(5-benzoylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-6-phenoxypyrimidin-4-yl)methylene)thiazolidine-2,4-dione	$C_{27}H_{23}N_5O_4S$	513.568	17	7
150	(Z)-5-((6-phenoxy-2-(5-(phenylsulfonyl)hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione	$C_{26}H_{23}N_5O_5S_2$	549.621	18	7
151	(Z)-5-(4-((2,4-dioxothiazolidin-5-ylidene)methyl)-6-phenoxypyrimidin-2-yl)-N-phenylhexahydropyrrolo[3,4-c]pyrrole-2(1H)-carboxamide	$C_{27}H_{24}N_6O_4S$	528.582	19	7
152	(Z)-6-(4-((2,4-dioxothiazolidin-5-ylidene)methyl)-6-phenoxypyrimidin-2-yl)-N-phenyl-2,6-diazaspiro[3.3]heptane-2-carboxamide	$C_{26}H_{22}N_6O_4S$	514.556	20	7
153	(Z)-5-((2-(6-benzoyl-2,6-diazaspiro[3.3]heptan-2-yl)-6-phenoxypyrimidin-4-yl)methylene)thiazolidine-2,4-dione	$C_{26}H_{21}N_5O_4S$	499.541	21	7
154	(Z)-5-((6-phenoxy-2-(6-(phenylsulfonyl)-2,6-diazaspiro[3.3]heptan-2-yl)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione	$C_{25}H_{21}N_5O_5S_2$	535.595	22	7
155	(Z)-5-((6-(benzyloxy)-2-(4-phenylpiperazin-1-yl)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione	$C_{25}H_{23}N_5O_3S$	473.547	1	8

TABLE 3-continued

Additional prophetic embodiments of the invention.

No.	Chemical Name	Formula	Mol. Weight	Reactant A	Reactant B
156	(Z)-5-((6-(benzyloxy)-2-(4-(pyridin-3-yl)piperazin-1-yl)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione	$C_{24}H_{22}N_6O_3S$	474.535	2	8
157	(Z)-5-((6-(benzyloxy)-2-(4-(pyrimidin-5-yl)piperazin-1-yl)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione	$C_{23}H_{21}N_7O_3S$	475.523	3	8
158	(Z)-5-((6-(benzyloxy)-2-(4-(pyrimidin-2-yl)piperazin-1-yl)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione	$C_{23}H_{21}N_7O_3S$	475.523	4	8
159	(Z)-4-(4-(benzyloxy)-6-((2,4-dioxothiazolidin-5-ylidene)methyl)pyrimidin-2-yl)-N-phenylpiperazine-1-carboxamide	$C_{26}H_{24}N_6O_4S$	516.572	5	8
160	(Z)-5-((6-(benzyloxy)-2-(4-(1-ethylpiperidin-4-yl)piperazin-1-yl)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione	$C_{26}H_{32}N_6O_3S$	508.636	6	8
161	(Z)-5-((6-(benzyloxy)-2-(4-(pyridin-4-yl)-1,4-diazepan-1-yl)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione	$C_{25}H_{24}N_6O_3S$	488.561	7	8
162	(Z)-5-((2-(4-(benzo[d]oxazol-2-yl)-1,4-diazepan-1-yl)-6-(benzyloxy)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione	$C_{27}H_{24}N_6O_4S$	528.582	8	8
163	(Z)-4-(4-(benzyloxy)-6-((2,4-dioxothiazolidin-5-ylidene)methyl)pyrimidin-2-yl)-N-phenyl-1,4-diazepane-1-carboxamide	$C_{27}H_{26}N_6O_4S$	530.598	9	8
164	(Z)-5-((6-(benzyloxy)-2-(4-(6-methyl-2-(pyrrolidin-1-yl)pyrimidin-4-yl)-1,4-diazepan-1-yl)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione	$C_{29}H_{32}N_8O_3S$	572.681	10	8
165	(Z)-5-((6-(benzyloxy)-2-((2-(diethylamino)ethyl)(methyl)amino)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione	$C_{22}H_{27}N_5O_3S$	441.546	11	8
166	(Z)-N-(2-((4-(benzyloxy)-6-((2,4-dioxothiazolidin-5-ylidene)methyl)pyrimidin-2-yl)amino)ethyl)isoquinoline-5-sulfonamide	$C_{26}H_{22}N_6O_5S_2$	562.62	12	8
167	(Z)-N-(2-((4-(benzyloxy)-6-((2,4-dioxothiazolidin-5-ylidene)methyl)pyrimidin-2-yl)amino)ethyl)benzamide	$C_{24}H_{21}N_5O_4S$	475.52	13	8
168	(Z)-5-((6-(benzyloxy)-2-((2-(4-oxo-3,4-dihydroquinazolin-2-yl)ethyl)amino)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione	$C_{25}H_{20}N_6O_4S$	500.529	14	8
169	(Z)-5-((2-(4-benzoylpiperazin-1-yl)-6-(benzyloxy)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione	$C_{26}H_{23}N_5O_4S$	501.557	15	8
170	(Z)-5-((6-(benzyloxy)-2-(4-(phenylsulfonyl)piperazin-1-yl)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione	$C_{25}H_{23}N_5O_5S_2$	537.611	16	8
171	(Z)-5-((2-(5-benzoylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-6-(benzyloxy)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione	$C_{28}H_{25}N_5O_4S$	527.594	17	8
172	(Z)-5-((6-(benzyloxy)-2-(5-(phenylsulfonyl)hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione	$C_{27}H_{25}N_5O_5S_2$	563.648	18	8
173	(Z)-5-(4-(benzyloxy)-6-((2,4-dioxothiazolidin-5-ylidene)methyl)pyrimidin-2-yl)-N-phenylhexahydropyrrolo[3,4-c]pyrrole-2(1H)-carboxamide	$C_{28}H_{26}N_6O_4S$	542.609	19	8
174	(Z)-6-(4-(benzyloxy)-6-((2,4-dioxothiazolidin-5-ylidene)methyl)pyrimidin-2-yl)-N-phenyl-2,6-diazaspiro[3.3]heptane-2-carboxamide	$C_{27}H_{24}N_6O_4S$	528.582	20	8
175	(Z)-5-((2-(6-benzoyl-2,6-diazaspiro[3.3]heptan-2-yl)-6-(benzyloxy)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione	$C_{27}H_{23}N_5O_4S$	513.568	21	8
176	(Z)-5-((6-(benzyloxy)-2-(6-(phenylsulfonyl)-2,6-diazaspiro[3.3]heptan-2-yl)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione	$C_{26}H_{23}N_5O_5S_2$	549.621	22	8
177	(Z)-5-((6-(2-methoxyethoxy)-2-(4-phenylpiperazin-1-yl)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione	$C_{21}H_{23}N_5O_4S$	441.503	1	9
178	(Z)-5-((6-(2-methoxyethoxy)-2-(4-(pyridin-3-yl)piperazin-1-yl)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione	$C_{20}H_{22}N_6O_4S$	442.491	2	9
179	(Z)-5-((6-(2-methoxyethoxy)-2-(4-(pyrimidin-5-yl)piperazin-1-yl)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione	$C_{19}H_{21}N_7O_4S$	443.48	3	9
180	(Z)-5-((6-(2-methoxyethoxy)-2-(4-(pyrimidin-2-yl)piperazin-1-yl)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione	$C_{19}H_{21}N_7O_4S$	443.48	4	9
181	(Z)-4-(4-((2,4-dioxothiazolidin-5-ylidene)methyl)-6-(2-methoxyethoxy)pyrimidin-2-yl)-N-phenylpiperazine-1-carboxamide	$C_{22}H_{24}N_6O_5S$	484.528	5	9

TABLE 3-continued

Additional prophetic embodiments of the invention.

No.	Chemical Name	Formula	Mol. Weight	Reactant A	Reactant B
182	(Z)-5-((2-(4-(1-ethylpiperidin-4-yl)piperazin-1-yl)-6-(2-methoxyethoxy)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione	$C_{22}H_{32}N_6O_4S$	476.592	6	9
183	(Z)-5-((6-(2-methoxyethoxy)-2-(4-(pyridin-4-yl)-1,4-diazepan-1-yl)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione	$C_{21}H_{24}N_6O_4S$	456.518	7	9
184	(Z)-5-((2-(4-(benzo[d]oxazol-2-yl)-1,4-diazepan-1-yl)-6-(2-methoxyethoxy)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione	$C_{23}H_{24}N_6O_5S$	496.539	8	9
185	(Z)-4-(4-((2,4-dioxothiazolidin-5-ylidene)methyl)-6-(2-methoxyethoxy)pyrimidin-2-yl)-N-phenyl-1,4-diazepane-1-carboxamide	$C_{23}H_{26}N_6O_5S$	498.555	9	9
186	(Z)-5-((6-(2-methoxyethoxy)-2-(4-(6-methyl-2-(pyrrolidin-1-yl)pyrimidin-4-yl)-1,4-diazepan-1-yl)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione	$C_{25}H_{32}N_8O_4S$	540.638	10	9
187	(Z)-5-((2-((2-(diethylamino)ethyl)(methyl)amino)-6-(2-methoxyethoxy)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione	$C_{18}H_{27}N_5O_4S$	409.503	11	9
188	(Z)-N-(2-((4-((2,4-dioxothiazolidin-5-ylidene)methyl)-6-(2-methoxyethoxy)pyrimidin-2-yl)amino)ethyl)isoquinoline-5-sulfonamide	$C_{22}H_{22}N_6O_6S_2$	530.577	12	9
189	(Z)-N-(2-((4-((2,4-dioxothiazolidin-5-ylidene)methyl)-6-(2-methoxyethoxy)pyrimidin-2-yl)amino)ethyl)benzamide	$C_{20}H_{21}N_5O_5S$	443.476	13	9
190	(Z)-5-((6-(2-methoxyethoxy)-2-((2-(4-oxo-3,4-dihydroquinazolin-2-yl)ethyl)amino)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione	$C_{21}H_{20}N_6O_5S$	468.486	14	9
191	(Z)-5-((2-(4-benzoylpiperazin-1-yl)-6-(2-methoxyethoxy)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione	$C_{22}H_{23}N_5O_5S$	469.514	15	9
192	(Z)-5-((6-(2-methoxyethoxy)-2-(4-(phenylsulfonyl)piperazin-1-yl)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione	$C_{21}H_{23}N_5O_6S_2$	505.567	16	9
193	(Z)-5-((2-(5-benzoylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-6-(2-methoxyethoxy)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione	$C_{24}H_{25}N_5O_5S$	495.551	17	9
194	(Z)-5-((6-(2-methoxyethoxy)-2-(5-(phenylsulfonyl)hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione	$C_{23}H_{25}N_5O_6S_2$	531.605	18	9
195	(Z)-5-(4-((2,4-dioxothiazolidin-5-ylidene)methyl)-6-(2-methoxyethoxy)pyrimidin-2-yl)-N-phenylhexahydropyrrolo[3,4-c]pyrrole-2(1H)-carboxamide	$C_{24}H_{26}N_6O_5S$	510.565	19	9
196	(Z)-6-(4-((2,4-dioxothiazolidin-5-ylidene)methyl)-6-(2-methoxyethoxy)pyrimidin-2-yl)-N-phenyl-2,6-diazaspiro[3.3]heptane-2-carboxamide	$C_{23}H_{24}N_6O_5S$	496.539	20	9
197	(Z)-5-((2-(6-benzoyl-2,6-diazaspiro[3.3]heptan-2-yl)-6-(2-methoxyethoxy)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione	$C_{23}H_{23}N_5O_5S$	481.524	21	9
198	(Z)-5-((6-(2-methoxyethoxy)-2-(6-(phenylsulfonyl)-2,6-diazaspiro[3.3]heptan-2-yl)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione	$C_{22}H_{23}N_5O_6S_2$	517.578	22	9
199	(Z)-5-((6-(2-(dimethylamino)ethoxy)-2-(4-phenylpiperazin-1-yl)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione	$C_{22}H_{26}N_6O_3S$	454.545	1	10
200	(Z)-5-((6-(2-(dimethylamino)ethoxy)-2-(4-(pyridin-3-yl)piperazin-1-yl)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione	$C_{21}H_{25}N_7O_3S$	455.533	2	10
201	(Z)-5-((6-(2-(dimethylamino)ethoxy)-2-(4-(pyrimidin-5-yl)piperazin-1-yl)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione	$C_{20}H_{24}N_8O_3S$	456.521	3	10
202	(Z)-5-((6-(2-(dimethylamino)ethoxy)-2-(4-(pyrimidin-2-yl)piperazin-1-yl)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione	$C_{20}H_{24}N_8O_3S$	456.521	4	10
203	(Z)-4-(4-(2-(dimethylamino)ethoxy)-6-((2,4-dioxothiazolidin-5-ylidene)methyl)pyrimidin-2-yl)-N-phenylpiperazine-1-carboxamide	$C_{23}H_{27}N_7O_4S$	497.57	5	10
204	(Z)-5-((6-(2-(dimethylamino)ethoxy)-2-(4-(1-ethylpiperidin-4-yl)piperazin-1-yl)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione	$C_{23}H_{35}N_7O_3S$	489.634	6	10
205	(Z)-5-((6-(2-(dimethylamino)ethoxy)-2-(4-(pyridin-4-yl)-1,4-diazepan-1-yl)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione	$C_{22}H_{27}N_7O_3S$	469.56	7	10

TABLE 3-continued

Additional prophetic embodiments of the invention.

No.	Chemical Name	Formula	Mol. Weight	Reactant A	Reactant B
206	(Z)-5-((2-(4-(benzo[d]oxazol-2-yl)-1,4-diazepan-1-yl)-6-(2-(dimethylamino)ethoxy)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione	$C_{24}H_{27}N_7O_4S$	509.581	8	10
207	(Z)-4-(4-(2-(dimethylamino)ethoxy)-6-((2,4-dioxothiazolidin-5-ylidene)methyl)pyrimidin-2-yl)-N-phenyl-1,4-diazepane-1-carboxamide	$C_{24}H_{29}N_7O_4S$	511.597	9	10
208	(Z)-5-((6-(2-(dimethylamino)ethoxy)-2-(4-(6-methyl-2-(pyrrolidin-1-yl)pyrimidin-4-yl)-1,4-diazepan-1-yl)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione	$C_{26}H_{35}N_9O_3S$	553.68	10	10
209	(Z)-5-((2-((2-(diethylamino)ethyl)(methyl)amino)-6-(2-(dimethylamino)ethoxy)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione	$C_{19}H_{30}N_6O_3S$	422.545	11	10
210	(Z)-N-(2-((4-(2-(dimethylamino)ethoxy)-6-((2,4-dioxothiazolidin-5-ylidene)methyl)pyrimidin-2-yl)amino)ethyl)isoquinoline-5-sulfonamide	$C_{23}H_{25}N_7O_5S_2$	543.619	12	10
211	(Z)-N-(2-((4-(2-(dimethylamino)ethoxy)-6-((2,4-dioxothiazolidin-5-ylidene)methyl)pyrimidin-2-yl)amino)ethyl)benzamide	$C_{21}H_{24}N_6O_4S$	456.518	13	10
212	(Z)-5-((6-(2-(dimethylamino)ethoxy)-2-((2-(4-oxo-3,4-dihydroquinazolin-2-yl)ethyl)amino)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione	$C_{22}H_{23}N_7O_4S$	481.528	14	10
213	(Z)-5-((2-(4-benzoylpiperazin-1-yl)-6-(2-(dimethylamino)ethoxy)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione	$C_{23}H_{26}N_6O_4S$	482.555	15	10
214	(Z)-5-((6-(2-(dimethylamino)ethoxy)-2-(4-(phenylsulfonyl)piperazin-1-yl)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione	$C_{22}H_{26}N_6O_5S_2$	518.609	16	10
215	(Z)-5-((2-(5-benzoylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-6-(2-(dimethylamino)ethoxy)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione	$C_{25}H_{28}N_6O_4S$	508.593	17	10
216	(Z)-5-((6-(2-(dimethylamino)ethoxy)-2-(5-(phenylsulfonyl)hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione	$C_{24}H_{28}N_6O_5S_2$	544.646	18	10
217	(Z)-5-(4-(2-(dimethylamino)ethoxy)-6-((2,4-dioxothiazolidin-5-ylidene)methyl)pyrimidin-2-yl)-N-phenylhexahydropyrrolo[3,4-c]pyrrole-2(1H)-carboxamide	$C_{25}H_{29}N_7O_4S$	523.607	19	10
218	(Z)-6-(4-(2-(dimethylamino)ethoxy)-6-((2,4-dioxothiazolidin-5-ylidene)methyl)pyrimidin-2-yl)-N-phenyl-2,6-diazaspiro[3.3]heptane-2-carboxamide	$C_{24}H_{27}N_7O_4S$	509.581	20	10
219	(Z)-5-((2-(6-benzoyl-2,6-diazaspiro[3.3]heptan-2-yl)-6-(2-(dimethylamino)ethoxy)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione	$C_{24}H_{26}N_6O_4S$	494.566	21	10
220	(Z)-5-((6-(2-(dimethylamino)ethoxy)-2-(6-(phenylsulfonyl)-2,6-diazaspiro[3.3]heptan-2-yl)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione	$C_{23}H_{26}N_6O_5S_2$	530.62	22	10
221	(Z)-5-((4-(4-phenylpiperazin-1-yl)pyrimidin-2-yl)methylene)thiazolidine-2,4-dione	$C_{18}H_{17}N_5O_2S$	367.425	1	11
222	(Z)-5-((4-(4-(pyridin-3-yl)piperazin-1-yl)pyrimidin-2-yl)methylene)thiazolidine-2,4-dione	$C_{17}H_{16}N_6O_2S$	368.413	2	11
223	(Z)-5-((4-(4-(pyrimidin-5-yl)piperazin-1-yl)pyrimidin-2-yl)methylene)thiazolidine-2,4-dione	$C_{16}H_{15}N_7O_2S$	369.401	3	11
224	(Z)-5-((4-(4-(pyrimidin-2-yl)piperazin-1-yl)pyrimidin-2-yl)methylene)thiazolidine-2,4-dione	$C_{16}H_{15}N_7O_2S$	369.401	4	11
225	(Z)-4-(2-((2,4-dioxothiazolidin-5-ylidene)methyl)pyrimidin-4-yl)-N-phenylpiperazine-1-carboxamide	$C_{19}H_{18}N_6O_3S$	410.45	5	11
226	(Z)-5-((4-(4-(1-ethylpiperidin-4-yl)piperazin-1-yl)pyrimidin-2-yl)methylene)thiazolidine-2,4-dione	$C_{19}H_{26}N_6O_2S$	402.514	6	11
227	(Z)-5-((4-(4-(pyridin-4-yl)-1,4-diazepan-1-yl)pyrimidin-2-yl)methylene)thiazolidine-2,4-dione	$C_{18}H_{18}N_6O_2S$	382.44	7	11
228	(Z)-5-((4-(4-(benzo[d]oxazol-2-yl)-1,4-diazepan-1-yl)pyrimidin-2-yl)methylene)thiazolidine-2,4-dione	$C_{20}H_{18}N_6O_3S$	422.46	8	11
229	(Z)-4-(2-((2,4-dioxothiazolidin-5-ylidene)methyl)pyrimidin-4-yl)-N-phenyl-1,4-diazepane-1-carboxamide	$C_{20}H_{20}N_6O_3S$	424.476	9	11
230	(Z)-5-((4-(4-(6-methyl-2-(pyrrolidin-1-yl)pyrimidin-4-yl)-1,4-diazepan-1-yl)pyrimidin-2-yl)methylene)thiazolidine-2,4-dione	$C_{22}H_{26}N_8O_2S$	466.559	10	11
231	(Z)-5-((4-((2-(diethylamino)ethyl)(methyl)amino)pyrimidin-2-yl)methylene)thiazolidine-2,4-dione	$C_{15}H_{21}N_5O_2S$	335.425	11	11

TABLE 3-continued

Additional prophetic embodiments of the invention.

No.	Chemical Name	Formula	Mol. Weight	Reactant A	Reactant B
232	(Z)-N-(2-((2-((2,4-dioxothiazolidin-5-ylidene)methyl)pyrimidin-4-yl)amino)ethyl)isoquinoline-5-sulfonamide	$C_{19}H_{16}N_6O_4S_2$	456.498	12	11
233	(Z)-N-(2-((2-((2,4-dioxothiazolidin-5-ylidene)methyl)pyrimidin-4-yl)amino)ethyl)benzamide	$C_{17}H_{15}N_5O_3S$	369.398	13	11
234	(Z)-5-((4-((2-(4-oxo-3,4-dihydroquinazolin-2-yl)ethyl)amino)pyrimidin-2-yl)methylene)thiazolidine-2,4-dione	$C_{18}H_{14}N_6O_3S$	394.407	14	11
235	(Z)-5-((4-(4-benzoylpiperazin-1-yl)pyrimidin-2-yl)methylene)thiazolidine-2,4-dione	$C_{19}H_{17}N_5O_3S$	395.435	15	11
236	(Z)-5-((4-(4-(phenylsulfonyl)piperazin-1-yl)pyrimidin-2-yl)methylene)thiazolidine-2,4-dione	$C_{18}H_{17}N_5O_4S_2$	431.489	16	11
237	(Z)-5-((4-(5-benzoylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)pyrimidin-2-yl)methylene)thiazolidine-2,4-dione	$C_{21}H_{19}N_5O_3S$	421.472	17	11
238	(Z)-5-((4-(5-(phenylsulfonyl)hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)pyrimidin-2-yl)methylene)thiazolidine-2,4-dione	$C_{20}H_{19}N_5O_4S_2$	457.526	18	11
239	(Z)-5-(2-((2,4-dioxothiazolidin-5-ylidene)methyl)pyrimidin-4-yl)-N-phenylhexahydropyrrolo[3,4-c]pyrrole-2(1H)-carboxamide	$C_{21}H_{20}N_6O_3S$	436.487	19	11
240	(Z)-6-(2-((2,4-dioxothiazolidin-5-ylidene)methyl)pyrimidin-4-yl)-N-phenyl-2,6-diazaspiro[3.3]heptane-2-carboxamide	$C_{20}H_{18}N_6O_3S$	422.46	20	11
241	(Z)-5-((4-(6-benzoyl-2,6-diazaspiro[3.3]heptan-2-yl)pyrimidin-2-yl)methylene)thiazolidine-2,4-dione	$C_{20}H_{17}N_5O_3S$	407.446	21	11
242	(Z)-5-((4-(6-(phenylsulfonyl)-2,6-diazaspiro[3.3]heptan-2-yl)pyrimidin-2-yl)methylene)thiazolidine-2,4-dione	$C_{19}H_{17}N_5O_4S_2$	443.499	22	11
243	(Z)-5-((4-(4-phenylpiperazin-1-yl)-1,3,5-triazin-2-yl)methylene)thiazolidine-2,4-dione	$C_{17}H_{16}N_6O_2S$	368.413	1	12
244	(Z)-5-((4-(4-(pyridin-3-yl)piperazin-1-yl)-1,3,5-triazin-2-yl)methylene)thiazolidine-2,4-dione	$C_{16}H_{15}N_7O_2S$	369.401	2	12
245	(Z)-5-((4-(4-(pyrimidin-5-yl)piperazin-1-yl)-1,3,5-triazin-2-yl)methylene)thiazolidine-2,4-dione	$C_{15}H_{14}N_8O_2S$	370.389	3	12
246	(Z)-5-((4-(4-(pyrimidin-2-yl)piperazin-1-yl)-1,3,5-triazin-2-yl)methylene)thiazolidine-2,4-dione	$C_{15}H_{14}N_8O_2S$	370.389	4	12
247	(Z)-4-(4-((2,4-dioxothiazolidin-5-ylidene)methyl)-1,3,5-triazin-2-yl)-N-phenylpiperazine-1-carboxamide	$C_{18}H_{17}N_7O_3S$	411.438	5	12
248	(Z)-5-((4-(4-(1-ethylpiperidin-4-yl)piperazin-1-yl)-1,3,5-triazin-2-yl)methylene)thiazolidine-2,4-dione	$C_{18}H_{25}N_7O_2S$	403.502	6	12
249	(Z)-5-((4-(4-(pyridin-4-yl)-1,4-diazepan-1-yl)-1,3,5-triazin-2-yl)methylene)thiazolidine-2,4-dione	$C_{17}H_{17}N_7O_2S$	383.428	7	12
250	(Z)-5-((4-(4-(benzo[d]oxazol-2-yl)-1,4-diazepan-1-yl)-1,3,5-triazin-2-yl)methylene)thiazolidine-2,4-dione	$C_{19}H_{17}N_7O_3S$	423.448	8	12
251	(Z)-4-(4-((2,4-dioxothiazolidin-5-ylidene)methyl)-1,3,5-triazin-2-yl)-N-phenyl-1,4-diazepane-1-carboxamide	$C_{19}H_{19}N_7O_3S$	425.464	9	12
252	(Z)-5-((4-(4-(6-methyl-2-(pyrrolidin-1-yl)pyrimidin-4-yl)-1,4-diazepan-1-yl)-1,3,5-triazin-2-yl)methylene)thiazolidine-2,4-dione	$C_{21}H_{25}N_9O_2S$	467.547	10	12
253	(Z)-5-((4-((2-(diethylamino)ethyl)(methyl)amino)-1,3,5-triazin-2-yl)methylene)thiazolidine-2,4-dione	$C_{14}H_{20}N_6O_2S$	336.413	11	12
254	(Z)-N-(2-((4-((2,4-dioxothiazolidin-5-ylidene)methyl)-1,3,5-triazin-2-yl)amino)ethyl)isoquinoline-5-sulfonamide	$C_{18}H_{15}N_7O_4S_2$	457.486	12	12
255	(Z)-N-(2-((4-((2,4-dioxothiazolidin-5-ylidene)methyl)-1,3,5-triazin-2-yl)amino)ethyl)benzamide	$C_{16}H_{14}N_6O_3S$	370.386	13	12
256	(Z)-5-((4-((2-(4-oxo-3,4-dihydroquinazolin-2-yl)ethyl)amino)-1,3,5-triazin-2-yl)methylene)thiazolidine-2,4-dione	$C_{17}H_{13}N_7O_3S$	395.395	14	12
257	(Z)-5-((4-(4-benzoylpiperazin-1-yl)-1,3,5-triazin-2-yl)methylene)thiazolidine-2,4-dione	$C_{18}H_{16}N_6O_3S$	396.423	15	12
258	(Z)-5-((4-(4-(phenylsulfonyl)piperazin-1-yl)-1,3,5-triazin-2-yl)methylene)thiazolidine-2,4-dione	$C_{17}H_{16}N_6O_4S_2$	432.477	16	12
259	(Z)-5-((4-(5-benzoylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-1,3,5-triazin-2-yl)methylene)thiazolidine-2,4-dione	$C_{20}H_{18}N_6O_3S$	422.46	17	12
260	(Z)-5-((4-(5-(phenylsulfonyl)hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-1,3,5-triazin-2-yl)methylene)thiazolidine-2,4-dione	$C_{19}H_{18}N_6O_4S_2$	458.514	18	12

TABLE 3-continued

Additional prophetic embodiments of the invention.

No.	Chemical Name	Formula	Mol. Weight	Reactant A	Reactant B
261	(Z)-5-(4-((2,4-dioxothiazolidin-5-ylidene)methyl)-1,3,5-triazin-2-yl)-N-phenylhexahydropyrrolo[3,4-c]pyrrole-2(1H)-carboxamide	$C_{20}H_{19}N_7O_3S$	437.475	19	12
262	(Z)-6-(4-((2,4-dioxothiazolidin-5-ylidene)methyl)-1,3,5-triazin-2-yl)-N-phenyl-2,6-diazaspiro[3.3]heptane-2-carboxamide	$C_{19}H_{17}N_7O_3S$	423.448	20	12
263	(Z)-5-((4-(6-benzoyl-2,6-diazaspiro[3.3]heptan-2-yl)-1,3,5-triazin-2-yl)methylene)thiazolidine-2,4-dione	$C_{19}H_{16}N_6O_3S$	408.434	21	12
264	(Z)-5-((4-(6-(phenylsulfonyl)-2,6-diazaspiro[3.3]heptan-2-yl)-1,3,5-triazin-2-yl)methylene)thiazolidine-2,4-dione	$C_{18}H_{16}N_6O_4S_2$	444.487	22	12

In addition, it may be convenient or desirable to prepare, purify, and/or handle the active compound in a chemically protected form. The term "chemically protected form," as used herein, pertains to a compound in which one or more reactive functional groups are protected from undesirable chemical reactions (i.e., they have been modified with a protecting group).

By protecting a reactive functional group, reactions involving other unprotected reactive functional groups can be performed without affecting the protected group; the protecting group may be removed, usually in a subsequent step, without substantially affecting the remainder of the molecule. See, for example, *Protective Groups in Organic Synthesis* (T. Green and P. Wuts, Wiley, 1991), and *Protective Groups in Organic Synthesis* (T. Green and P. Wuts; 3rd Edition; John Wiley and Sons, 1999).

For example, a hydroxy group may be protected as an ether (—OR) or an ester (—OC(=O)R), for example, as: a t-butyl ether; a benzyl, benzhydryl (diphenylmethyl), or trityl (triphenylmethyl)ether; a trimethylsilyl or t-butyldimethylsilyl ether; or an acetyl ester (—OC(=O)CH_3, —OAc).

For example, an aldehyde or ketone group may be protected as an acetal or ketal, respectively, in which the carbonyl group (C(=O)) is converted to a diether ($C(OR)_2$), by reaction with, for example, a primary alcohol. The aldehyde or ketone group is readily regenerated by hydrolysis using a large excess of water in the presence of acid.

For example, an amine group may be protected, for example, as an amide (—NRC(=O)R) or a urethane (—NRC(=O)OR), for example, as: a methyl amide (—NHC(=O)CH_3); a benzyloxy amide (—NHC(=O)$OCH_2C_6H_5NHCbz$); as a t-butoxy amide (—NHC(=O)OC$(CH_3)_3$, —NHBoc); a 2-biphenyl-2-propoxy amide (—NHC(=O)$OC(CH_3)_2C_6H_4C_6H_5NHBoc$), as a 9-fluorenylmethoxy amide (—NHFmoc), as a 6-nitroveratryloxy amide (—NHNvoc), as a 2-trimethylsilylethyloxy amide (—NHTeoc), as a 2,2,2-trichloroethyloxy amide (—NHTroc), as an allyloxy amide (—NHAlloc), as a 2-(phenylsulfonyl)ethyloxy amide (—NHPsec); or, in suitable cases (e.g., cyclic amines), as a nitroxide radical.

For example, a carboxylic acid group may be protected as an ester or an amide, for example, as: a benzyl ester; a t-butyl ester; a methyl ester; or a methyl amide.

For example, a thiol group may be protected as a thioether (—SR), for example, as: a benzyl thioether; or an acetamidomethyl ether (—$SCH_2NHC(=O)CH_3$).

Pharmaceutical Compositions

One or more compounds of this invention can be administered to a mammal by themselves or in pharmaceutical compositions where they are mixed with suitable carriers or excipient(s) at doses to treat or ameliorate a disease or condition as described herein. Mixtures of these compounds can also be administered to the patient as a simple mixture or in suitable formulated pharmaceutical compositions. For example, one aspect of the invention relates to pharmaceutical composition comprising a therapeutically effective dose of a compound of formula I, or a pharmaceutically acceptable salt, solvate, enantiomer or stereoisomer thereof; and a pharmaceutically acceptable diluent or carrier.

Techniques for formulation and administration of the compounds of the instant application may be found in references well known to one of ordinary skill in the art, such as "Remington's Pharmaceutical Sciences," Mack Publishing Co., Easton, Pa., latest edition.

Suitable routes of administration may, for example, include oral, eyedrop, rectal, transmucosal, topical, or intestinal administration; parenteral delivery, including intramuscular, subcutaneous, intramedullary injections, as well as intrathecal, direct intraventricular, intravenous, intraperitoneal, intranasal, or intraocular injections.

Alternatively, one may administer a compound in a local rather than a systemic manner, for example, via injection of the compound directly into an edematous site, often in a depot or sustained release formulation.

Furthermore, one may administer a compound in a targeted drug delivery system, for example, in a liposome coated with endothelial-cell-specific antibody.

The pharmaceutical compositions of the present invention may be manufactured, e.g., by means of conventional mixing, dissolving, granulating, dragee-making, levigating, emulsifying, encapsulating, entrapping or lyophilizing processes.

Pharmaceutical compositions for use in accordance with the present invention thus may be formulated in a conventional manner using one or more physiologically acceptable carriers comprising excipients and auxiliaries which facilitate processing of the active compounds into preparations which can be used pharmaceutically. Proper formulation is dependent upon the route of administration chosen.

For injection, the agents of the invention may be formulated in aqueous solutions, preferably in physiologically compatible buffers such as Hanks' solution, Ringer's solution, or physiological saline buffer. For transmucosal administration, penetrants are used in the formulation appropriate to the barrier to be permeated. Such penetrants are generally known in the art.

For oral administration, the compounds can be formulated readily by combining the active compounds with pharmaceutically acceptable carriers well known in the art. Such carriers

enable the compounds of the invention to be formulated as tablets, pills, dragees, capsules, liquids, gels, syrups, slurries, suspensions and the like, for oral ingestion by a patient to be treated. Pharmaceutical preparations for oral use can be obtained by combining the active compound with a solid excipient, optionally grinding a resulting mixture, and processing the mixture of granules, after adding suitable auxiliaries, if desired, to obtain tablets or dragee cores. Suitable excipients include fillers such as sugars, including lactose, sucrose, mannitol, or sorbitol; cellulose preparations such as, for example, maize starch, wheat starch, rice starch, potato starch, gelatin, gum tragacanth, methyl cellulose, hydroxypropylmethyl-cellulose, sodium carboxymethylcellulose, and/or polyvinylpyrrolidone (PVP). If desired, disintegrating agents may be added, such as the cross-linked polyvinyl pyrrolidone, agar, or alginic acid or a salt thereof such as sodium alginate.

Dragee cores are provided with suitable coatings. For this purpose, concentrated sugar solutions may be used, which may optionally contain gum arabic, talc, polyvinyl pyrrolidone, carbopol gel, polyethylene glycol, and/or titanium dioxide, lacquer solutions, and suitable organic solvents or solvent mixtures. Dyestuffs or pigments may be added to the tablets or dragee coatings for identification or to characterize different combinations of active compound doses.

Pharmaceutical preparations which can be used orally include push-fit capsules made of gelatin, as well as soft, sealed capsules made of gelatin and a plasticizer, such as glycerol or sorbitol. The push-fit capsules can contain the active ingredients in admixture with filler such as lactose, binders such as starches, and/or lubricants such as talc or magnesium stearate and, optionally, stabilizers. In soft capsules, the active compounds may be dissolved or suspended in suitable liquids, such as fatty oils, liquid paraffin, or liquid polyethylene glycols. In addition, stabilizers may be added.

For buccal administration, the compositions may take the form of tablets or lozenges formulated in conventional manner.

For administration by inhalation, the compounds for use according to the present invention are conveniently delivered in the form of an aerosol spray presentation from pressurized packs or a nebuliser, with the use of a suitable propellant, e.g., dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas. In the case of pressurized aerosol the dosage unit may be determined by providing a valve to deliver a metered amount. Capsules and cartridges of e.g., gelatin for use in an inhaler or insufflator may be formulated containing a powder mix of the compound and a suitable powder base such as lactose or starch.

The compounds can be formulated for parenteral administration by injection, e.g., bolus injection or continuous infusion. Formulations for injection may be presented in unit dosage form, e.g., in ampoules or in multi-dose containers, with an added preservative. The compositions may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilizing and/or dispersing agents.

Pharmaceutical formulations for parenteral administration include aqueous solutions of the active compounds in water-soluble form. Additionally, suspensions of the active compounds may be prepared as appropriate oily injection suspensions. Suitable lipophilic solvents or vehicles include fatty oils such as sesame oil, or synthetic fatty acid esters, such as ethyl oleate or triglycerides, or liposomes. Aqueous injection suspensions may contain substances which increase the viscosity of the suspension, such as sodium carboxymethyl cellulose, sorbitol, or dextran. Optionally, the suspension may also contain suitable stabilizers or agents which increase the solubility of the compounds to allow for the preparation of highly concentrated solutions.

Alternatively, the active ingredient may be in powder form for reconstitution before use with a suitable vehicle, e.g., sterile pyrogen-free water.

The compounds may also be formulated in rectal compositions such as suppositories or retention enemas, e.g., containing conventional suppository bases such as cocoa butter or other glycerides.

In addition to the formulations described previously, the compounds may also be formulated as a depot preparation. Such long acting formulations may be administered by implantation (for example, subcutaneously or intramuscularly or by intramuscular injection). Thus, for example, the compounds may be formulated with suitable polymeric or hydrophobic materials (for example as an emulsion in an acceptable oil) or ion exchange resins, or as sparingly soluble derivatives (for example, as a sparingly soluble salt).

Alternatively, other delivery systems for hydrophobic pharmaceutical compounds may be employed. Liposomes and emulsions are examples of delivery vehicles or carriers for hydrophobic drugs. Certain organic solvents such as dimethysulfoxide also may be employed. Additionally, the compounds may be delivered using a sustained-release system, such as semi-permeable matrices of solid hydrophobic polymers containing the therapeutic agent. Various sustained-release materials have been established and are well known by those skilled in the art. Sustained-release capsules may, depending on their chemical nature, release the compounds for a few weeks up to over 100 days. Depending on the chemical nature and the biological stability of the therapeutic reagent, additional strategies for protein stabilization may be employed.

The pharmaceutical compositions may also comprise suitable solid or gel phase carriers or excipients. Examples of such carriers or excipients include but are not limited to calcium carbonate, calcium phosphate, various sugars, starches, cellulose derivatives, gelatin, and polymers, such as polyethylene glycols.

Methods of Treatment

Provided herein are methods of modulating the activity of CK1 and subtypes thereof, CK2, the Wnt pathway, and/or the TGFβ pathway. Also provided herein are methods of treating or preventing conditions and diseases the course of which can be influenced by modulating the activity of CK1 (e.g., CK1γ), CK2, the Wnt pathway, and/or the TGFβ pathway. Such methods typically comprise administering to a subject in need thereof a therapeutically effective amount of a compound or composition of the invention.

Also provided herein are methods of modulating the activity of PIM, such as PIM 1, PIM 2 or PIM 3, the JAK/STAT pathway, and/or the mTOR pathway, and/or Pgp. Also provided herein are methods of treating or preventing conditions and diseases, the course of which can be influenced by modulating the activity of the PIMs, the JAK/STAT pathway, and/or the mTOR pathway, and/or Pgp. Such methods typically comprise administering to a subject in need thereof a therapeutically effective amount of a compound or composition of the invention.

Various diseases, such as cancers, inflammation, and inflammatory diseases (e.g., osteoarthritis and rheumatoid arthritis), and neurological conditions (e.g., Alzheimer's disease) and neurodegeneration can be treated by administration of modulators of CK1 (e.g., CK1γ), CK2, the Wnt pathway and/or the TGFβ pathway. Bone-related diseases and condi-

tions, including osteoporosis and bone formation, also can be treated by administration of modulators of CK1 (e.g., CK1γ), CK2, the Wnt pathway and/or the TGFβ pathway. Bone restoration can be facilitated by administration of modulators of CK1 (e.g., CK1γ), CK2, the Wnt pathway and/or the TGFβ pathway. Additional conditions that can be treated by administration of modulators of CK1 (e.g., CK1γ), CK2, the Wnt pathway and/or the TGFβ pathway include hypoglycemia, metabolic syndrome and diabetes. Modulators of CK1 (e.g., CK1γ), CK2, the Wnt pathway and/or the TGFβ pathway are also useful for influencing apoptosis (e.g., increasing the rate of apoptosis in cancerous cells). Modulators of CK1 (e.g., CK1γ), CK2, the Wnt pathway and/or the TGFβ pathway are also useful in treatment or prevention of aberrant embryonic development.

Based at least on the fact that increased CK1γ has been found to be associated with certain cancers, a method for treating cancer in a subject comprises administering to the subject in need thereof a therapeutically effective amount of a compound that inhibits CK1γ. PIM1, PIM2, PIM3, the JAK/STAT pathway, and/or the mTOR pathway have also been found to be associated with certain cancers. Therefore, provided herein is a method for treating cancer comprising administering to a subject in need thereof a therapeutically effective amount of a compound that inhibits PIM1 and/or PIM2 and/or PIM3.

PIM1, PIM2, and PIM3 have also been associated with protecting Pgp from degradation, which can regulate drug efflux and drug resistance. Therefore, provided herein is a method for treating malignancies comprising administering to a subject in need thereof a therapeutically effective amount of a compound that inhibits PIM1 and/or PIM2 and/or PIM3 in conjunction with another drug, compound or material to abrogate resistance to the drug, compound or material.

The compounds described herein can be used for modulating cell proliferation, generally. Accordingly, diseases that may be treated include hyperproliferative diseases, such as benign cell growth and malignant cell growth.

Exemplary cancers that may be treated include leukemias, e.g., acute lymphoid leukemia and myeloid leukemia, and carcinomas, such as colorectal carcinoma and hepatocarcinoma. Other cancers include Acute Lymphoblastic Leukemia; Acute Lymphoblastic Leukemia; Acute Myeloid Leukemia; Acute Myeloid Leukemia; Adrenocortical Carcinoma Adrenocortical Carcinoma; AIDS-Related Cancers; AIDS-Related Lymphoma; Anal Cancer; Astrocytoma, Childhood Cerebellar; Astrocytoma, Childhood Cerebral; Basal Cell Carcinoma, see Skin Cancer (non-Melanoma); Bile Duct Cancer, Extrahepatic; Bladder Cancer; Bladder Cancer; Bone Cancer, osteosarcoma/Malignant Fibrous Histiocytoma; Brain Stem Glioma; Brain Tumor; Brain Tumor, Brain Stem Glioma; Brain Tumor, Cerebellar Astrocytoma; Brain Tumor, Cerebral Astrocytoma/Malignant Glioma; Brain Tumor, Ependymoma; Brain Tumor, Medulloblastoma; Brain Tumor, Supratentorial Primitive Neuroectodermal Tumors; Brain Tumor, Visual Pathway and Hypothalamic Glioma; Brain Tumor; Breast Cancer; Breast Cancer and Pregnancy; Breast Cancer; Breast Cancer, Male; Bronchial Adenomas/Carcinoids; Burkitt's Lymphoma; Carcinoid Tumor; Carcinoid Tumor, Gastrointestinal; Carcinoma of Unknown Primary; Central Nervous System Lymphoma, Primary; Cerebellar Astrocytoma; Cerebral Astrocytoma/Malignant Glioma; Cervical Cancer; Childhood Cancers; Chronic Lymphocytic Leukemia; Chronic Myelogenous Leukemia; Chronic Myeloproliferative Disorders; Colon Cancer; Colorectal Cancer; Cutaneous T-Cell Lymphoma, see Mycosis Fungoides and Sezary Syndrome; Endometrial Cancer; Ependymoma; Esophageal Cancer; Esophageal Cancer; Ewing's Family of Tumors; Extracranial Germ Cell Tumor; Extragonadal Germ Cell Tumor; Extrahepatic Bile Duct Cancer; Eye Cancer, Intraocular Melanoma; Eye Cancer, Retinoblastoma; Gallbladder Cancer; Gastric (Stomach) Cancer; Gastric (Stomach) Cancer; Gastrointestinal Carcinoid Tumor; Germ Cell Tumor, Extracranial; Germ Cell Tumor, Extragonadal; Germ Cell Tumor, Ovarian; Gestational Trophoblastic Tumor; Glioma; Glioma, Childhood Brain Stem; Glioma, Childhood Cerebral Astrocytoma; Glioma, Childhood Visual Pathway and Hypothalamic; Hairy Cell Leukemia; Head and Neck Cancer; Hematologic (Blood) Cancer, Hepatocellular (Liver) Cancer, Adult (Primary); Hepatocellular (Liver) Cancer, Childhood (Primary); Hodgkin's Lymphoma; Hodgkin's Lymphoma; Hodgkin's Lymphoma During Pregnancy; Hypopharyngeal Cancer; Hypothalamic and Visual Pathway Glioma; Intraocular Melanoma; Islet Cell Carcinoma (Endocrine Pancreas); Kaposi's Sarcoma; Kidney (Renal Cell) Cancer; Kidney Cancer; Laryngeal Cancer; Laryngeal Cancer; Leukemia, Acute Lymphoblastic; Leukemia, Acute Lymphoblastic; Leukemia, Acute Myeloid; Leukemia, Acute Myeloid; Leukemia, Chronic Lymphocytic; Leukemia; Chronic Myelogenous; Leukemia, Hairy Cell; Lip and Oral Cavity Cancer; Liver Cancer, Adult (Primary); Liver Cancer, Childhood (Primary); Lung Cancer, Non-Small Cell; Lung Cancer, Small Cell; Lymphoma, AIDS-Related; Lymphoma, Burkitt's; Lymphoma, Cutaneous T-Cell, see Mycosis Fungoides and Sezary Syndrome; Lymphoma, Hodgkin's; Lymphoma, Hodgkin's; Lymphoma, Hodgkin's During Pregnancy; Lymphoma, Non-Hodgkin's; Lymphoma, Non-Hodgkin's; Lymphoma, Non-Hodgkin's During Pregnancy; Lymphoma, Primary Central Nervous System; Macroglobulinemia, Waldenstrom's; Malignant Fibrous Histiocytoma of Bone/Osteosarcoma; Medulloblastoma; Melanoma; Melanoma, Intraocular (Eye); Merkel Cell Carcinoma; Mesothelioma, Adult Malignant; Mesothelioma; Metastatic Squamous Neck Cancer with Occult Primary; Multiple Endocrine Neoplasia Syndrome; Multiple Myeloma/Plasma Cell Neoplasm' Mycosis Fungoides; Myelodysplastic Syndromes; Myelodysplastic/Myeloproliferative Diseases; Myelogenous Leukemia, Chronic; Myeloid Leukemia, Adult Acute; Myeloid Leukemia, Childhood Acute; Myeloma, Multiple; Myeloproliferative Disorders, Chronic; Nasal Cavity and Paranasal Sinus Cancer; Nasopharyngeal Cancer; Nasopharyngeal Cancer; Neuroblastoma; Non-Hodgkin's Lymphoma; Non-Hodgkin's Lymphoma; Non-Hodgkin's Lymphoma During Pregnancy; Non-Small Cell Lung Cancer; Oral Cancer; Oral Cavity Cancer, Lip and; Oropharyngeal Cancer; Osteosarcoma/Malignant Fibrous Histiocytoma of Bone; Ovarian Cancer; Ovarian Epithelial Cancer; Ovarian Germ Cell Tumor; Ovarian Low Malignant Potential Tumor; Pancreatic Cancer; Islet Cell; Paranasal Sinus and Nasal Cavity Cancer; Parathyroid Cancer; Penile Cancer; Pheochromocytoma; Pineoblastoma and Supratentorial Primitive Neuroectodermal Tumors; Pituitary Tumor; Plasma Cell Neoplasm/Multiple Myeloma; Pleuropulmonary Blastoma; Pregnancy and Breast Cancer; Pregnancy and Hodgkin's Lymphoma; Pregnancy and Non-Hodgkin's Lymphoma; Primary Central Nervous System Lymphoma; Prostate Cancer; Rectal Cancer; Renal Cell (Kidney) Cancer; Renal Cell (Kidney) Cancer; Renal Pelvis and Ureter, Transitional Cell Cancer; Retinoblastoma; Rhabdomyosarcoma; Salivary Gland Cancer; Salivary Gland Cancer; Sarcoma, Ewing's Family of Tumors; Sarcoma, Kaposi's; Sarcoma, Soft Tissue; Sarcoma, Soft Tissue; Sarcoma, Uterine; Sezary Syndrome; Skin Cancer (non-Melanoma); Skin Cancer; Skin Cancer (Melanoma); Skin Carcinoma, Merkel Cell; Small Cell Lung Cancer;

Small Intestine Cancer; Soft Tissue Sarcoma; Soft Tissue Sarcoma; Squamous Cell Carcinoma, see Skin Cancer (non-Melanoma); Squamous Neck Cancer with Occult Primary, Metastatic; Stomach (Gastric) Cancer; Stomach (Gastric) Cancer; Supratentorial Primitive Neuroectodermal Tumors; T-Cell Lymphoma, Cutaneous, see Mycosis Fungoides and Sezary Syndrome; Testicular Cancer; Thymoma; Thymoma and Thymic Carcinoma; Thyroid Cancer; Thyroid Cancer; Transitional Cell Cancer of the Renal Pelvis and Ureter; Trophoblastic Tumor, Gestational; Unknown Primary Site, Carcinoma of; Unknown Primary Site, Cancer of; Unusual Cancers of Childhood; Ureter and Renal Pelvis, Transitional Cell Cancer; Urethral Cancer; Uterine Cancer, Endometrial; Uterine Sarcoma; Vaginal Cancer; Visual Pathway and Hypothalamic Glioma; Vulvar Cancer; Waldenstrom's Macroglobulinemia; Wilms' Tumor; and Women's Cancers.

Neurologic diseases that may be treated include epilepsy, schizophrenia, bipolar disorder or other psychological and/or psychiatric disorders, neuropathies, skeletal muscle atrophy, and neurodegenerative diseases, e.g., a neurodegenerative disease. Exemplary neurodegenerative diseases include. Alzheimer's disease, Amyotrophic Lateral Sclerosis (ALS), and Parkinson's disease. Another class of neurodegenerative diseases includes diseases caused at least in part by aggregation of poly-glutamine. Diseases of this class include: Huntington's Diseases, Spinalbulbar Muscular Atrophy (SBMA or Kennedy's Disease), Dentatorubropallidoluysian Atrophy (DRPLA), Spinocerebellar Ataxia 1 (SCAT), Spinocerebellar Ataxia 2 (SCA2), Machado-Joseph Disease (MJD; SCA3), Spinocerebellar Ataxia 6 (SCA6), Spinocerebellar Ataxia 7 (SCAT), and Spinocerebellar Ataxia 12 (SCA12).

Any other disease in which the Wnt pathway, TGFβ pathway, JAK/STAT pathway, the mTOR pathway, Pgp modulation, CK1, CK1γ, CK2, or PIMs plays a role may be treatable or preventable using compounds and methods described herein.

Dosage

As used herein, a "therapeutically effective amount" or "therapeutically effective dose" is an amount of a compound of the invention or a combination of two or more such compounds, which inhibits, totally or partially, the progression of the condition or alleviates, at least partially, one or more symptoms of the condition. A therapeutically effective amount can also be an amount which is prophylactically effective. The amount which is therapeutically effective will depend upon the patient's size and gender, the condition to be treated, the severity of the condition and the result sought. For a given patient, a therapeutically effective amount may be determined by methods known to those of skill in the art.

A therapeutically effective dose refers to that amount of the compound that results in amelioration of symptoms in a patient. Toxicity and therapeutic efficacy of such compounds can be determined by standard pharmaceutical procedures in cell cultures or experimental animals, e.g., for determining the maximum tolerated dose (MTD) and the ED_{50} (effective dose for 50% maximal response). The dose ratio between toxic and therapeutic effects is the therapeutic index and it can be expressed as the ratio between MTD and ED_{50}. The data obtained from these cell culture assays and animal studies can be used in formulating a range of dosage for use in humans. The dosage of such compounds lies preferably within a range of circulating concentrations that include the ED_{50} with little or no toxicity. The dosage may vary within this range depending upon the dosage form employed and the route of administration utilized. The exact formulation, route of administration and dosage can be chosen by the individual physician in view of the patient's condition. In the treatment of crises, the administration of an acute bolus or an infusion approaching the MTD may be required to obtain a rapid response.

Dosage amount and interval may be adjusted individually to provide plasma levels of the active moiety which are sufficient to maintain the CK1, CK1γ, CK2, Piml-3, Wnt pathway, TGFβ pathway, JAK/STAT pathway, mTOR pathway, or Pgp modulating effects, or minimal effective concentration (MEC). The MEC will vary for each compound but can be estimated from in vitro data. Dosages necessary to achieve the MEC will depend on individual characteristics and route of administration. HPLC assays or bioassays can be used to determine plasma concentrations.

Dosage intervals can also be determined using the MEC value. Compounds should be administered using a regimen which maintains plasma levels above the MEC for 10-90% of the time, preferably between 30-90% and most preferably between 50-90% until the desired amelioration of symptoms is achieved. In cases of local administration or selective uptake, the effective local concentration of the drug may not be related to plasma concentration.

The amount of composition administered will, of course, be dependent on the subject being treated, on the subject's weight, the severity of the affliction, the manner of administration and the judgment of the prescribing physician.

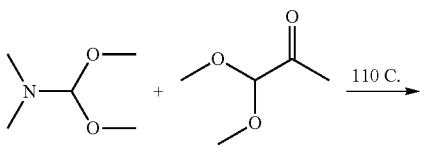
Kits

The compounds and compositions of the invention (e.g., compounds and compositions of formula I) may, if desired, be presented in a pack or dispenser device which may contain one or more unit dosage forms containing the active ingredient. The pack may for example comprise metal or plastic foil, such as a blister pack. The pack or dispenser device may be accompanied by instructions for administration. Compositions comprising a compound of the invention formulated in a compatible pharmaceutical carrier may also be prepared, placed in an appropriate container, and labelled for treatment of an indicated condition. Instructions for use may also be provided.

EXEMPLIFICATION

The invention now being generally described, it will be more readily understood by reference to the following examples, which are included merely for purposes of illustration of certain aspects and embodiments of the present invention, and are not intended to limit the invention. The geometric isomers depicted below are believed to be correct, but final structural assignment will be made via 2-D NMR experiments. Although the exemplary compounds described below are believed to be the Z-geometric isomers, the E-geometric isomers and mixtures of the E- and Z-isomers are also contemplated by the present disclosure.

Example 1



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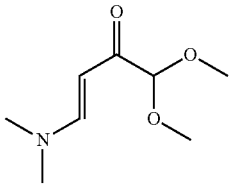
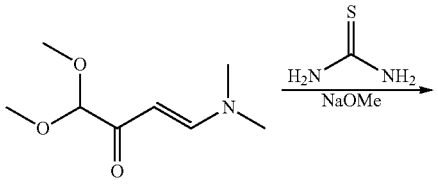


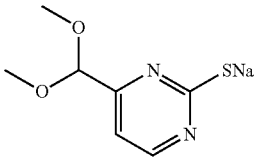
1

(E)-4-(dimethylamino)-1,1-dimethoxybut-3-en-2-one (1): 1,1-dimethoxy-N,N-dimethylmethanamine (100 g, 839 mmol, 1.02 equiv.) and 1,1-dimethoxypropan-2-one (97 g, 821 mmol) were added and stirred at 110° C. for 3 hours. The produced methanol was removed by a Dean-Stark apparatus. After the solution was cooled to room temperature, the remaining volatile materials were removed in vacuo to provide 130 g of the crude product, (E)-4-(dimethylamino)-1,1-dimethoxybut-3-en-2-one (1) (130 g, 143 g theoretical, 91%). LC-MS m/z 283 (M+1). Reference: WO 2006/0097341A1, pg 67.

Example 2



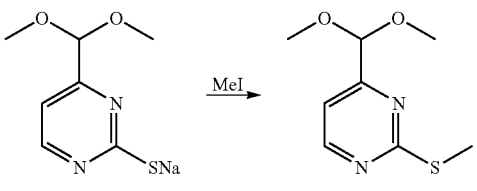
1



2

Sodium 4-(dimethoxymethyl)pyrimidine-2-thiolate (2): A solution of thiourea (64.7 g, 850 mmol, 1.13 equiv.), sodium methanolate (95%, 40.5 g, 751 mmol, 1.0 equiv.) in methanol (500 mL, 1.5 M) was stirred at room temperature for 30 minutes. A solution of (E)-4-(dimethylamino)-1,1-dimethoxybut-3-en-2-one (1) (130 g, 751 mmol) in methanol (200 mL) was added and the reaction stirred at room temperature for 2 h. The crude sodium 4-(dimethoxymethyl)pyrimidine-2-thiolate (2) was used directly in the next step without further purification. LC-MS m/z 209 (M+1). Reference: WO 2006/0097341A1, pg 67.

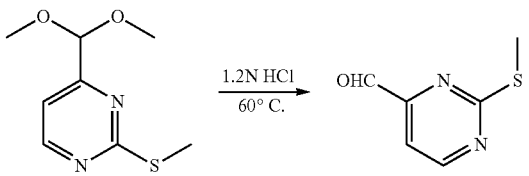
Example 3



2 3

4-(dimethoxymethyl)-2-(methylthio)pyrimidine (3): Iodomethane (128 g, 902 mmol, 1.20 equiv.) was added carefully to the crude solution of sodium 4-(dimethoxymethyl) pyrimidine-2-thiolate (2) (156 g, 751 mmol) in methanol (700 mL, 1.1 M) while maintaining the reaction temperature below 28° C. using an ice-water bath for cooling. The resulting mixture was stirred at room temperature for 16 h. After removal of the solvent under reduced pressure, the residue was diluted with water (300 mL) and extracted with ethyl acetate (2×150 mL). The combined organic layer was concentrated under reduced pressure and the crude residue purified by passing through a short silica gel pad and washing with diethyl ether (200 mL) to afford 4-(dimethoxymethyl)-2-(methylthio)pyrimidine (3) as a brown oil (53.7 g, 150 g theoretical, 35.7%). LC-MS m/z 201 (M+1). Reference: WO 2006/0097341A1, pg 67.

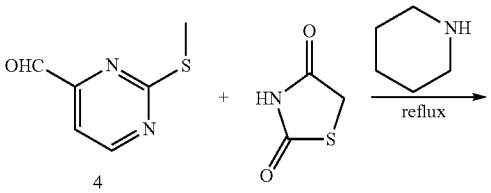
Example 4



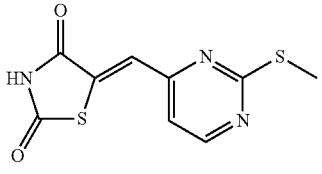
3 4

2-(methylthio)pyrimidine-4-carbaldehyde (4): 4-(dimethoxymethyl)-2-(methylthio)pyrimidine (3) (53.7 g, 268 mmol) was added carefully to 1.2 N aqueous HCl (300 mL, 268 mmol, 1.0 equiv.) and stirred at 60° C. for 3 hours. The reaction mixture was then cooled to room temperature and neutralized by the slow addition of solid sodium bicarbonate. The crude mixture was extracted with diethyl ether (3×150 mL) and the combined organic layer was concentrated under reduced pressure to afford 2-(methylthio)pyrimidine-4-carbaldehyde (4) as a yellow solid (14.2 g, 41.5 g theoretical, 34%). LC-MS m/z 155 (M+1). Reference: WO 2006/009734 A1, pg 67.

Example 5



4

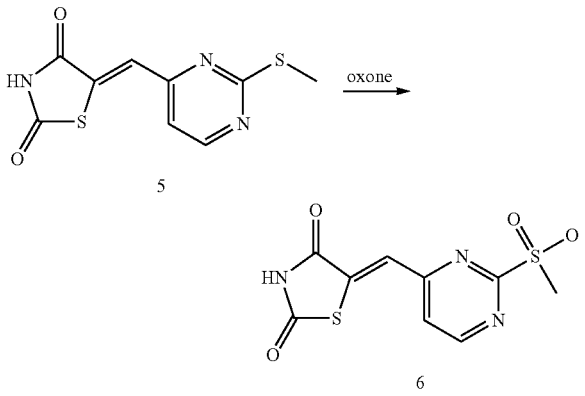


5

(Z)-5-((2-(methylthio)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione (5): A 40 mL round-bottomed vial was charged with 2-(methylthio)pyrimidine-4-carbaldehyde (4) (771 mg, 5 mmol), thiazolidine-2,4-dione (586 mg, 5 mmol, 1.0 equiv.), and piperidine (400 μL, 4 mmol, 0.8 equiv.) in

ethanol (20 mL, 0.25 M). The reaction mixture was heated to 80° C. and shaken for 20 h. The resulting yellow precipitate was isolated by filtration and washed with ethanol (1×20 mL) and dried in vacuo to afford (Z)-5-((2-(methylthio)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione (5) as a yellow solid (550 mg, 898 mg theoretical, 61%). LC-MS m/z 254 (M+1).

Example 6

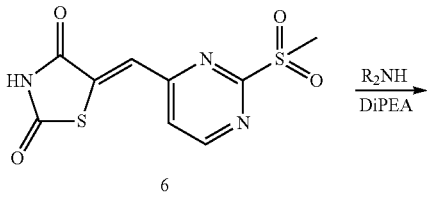


5

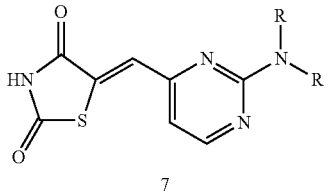
6

(Z)-5-((2-(methylsulfonyl)pyrimidin-4-yl)methylene) thiazolidine-2,4-dione (6): A mixture of (Z)-5-((2-(methylthio)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione (5) (3.5 g, 13.82 mmol) in THF (100 mL, 0.13 M) was treated with a solution of oxone (25.8 g, 41.5 mmol, 3.0 equiv.) in water (175 mL). The resulting mixture was stirred at room temperature for 48 h. The resulting precipitate was filtered and washed with water (20 mL) and diethyl ether (20 mL) to afford (Z)-5-((2-(methylsulfonyl)pyrimidin-4-yl)methylene) thiazolidine-2,4-dione (6) as a solid (2.48 g, 3.94 g theoretical, 63%). LC-MS m/z 286 (M+1).

Example 7



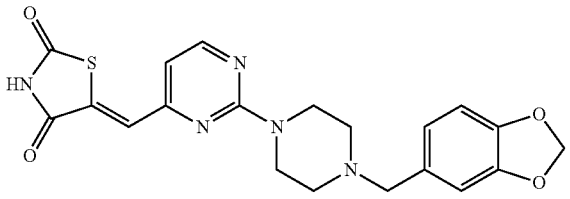
6



7

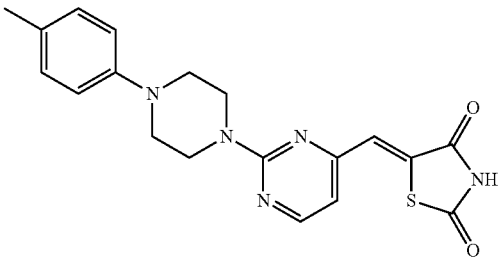
General Displacement Procedure 1: 2 dram round bottomed vials were charged with (Z)-5-((2-(methylsulfonyl) pyrimidin-4-yl)methylene)thiazolidine-2,4-dione (6) (25 mg, 0.0877 mmol), DMSO (1 mL, 0.08 M), diisopropylethylamine (50 μL, 0.288 mmol, 3.2 equiv.), and the appropriate amine (0.0877 mmol, 1.0 equiv.). The reaction mixture was heated to 120° C. and shaken for 16 h. The solvent was removed under reduced pressure (Genevac HT-4) and the crude residues were purified using reverse phase HPLC (MS-triggered fraction collection) with an acetonitrile/water gradient and trifluoroacetic acid as a modifier. The pure fractions were then concentrated under reduced pressure (Genevac HT-4).

Example 8



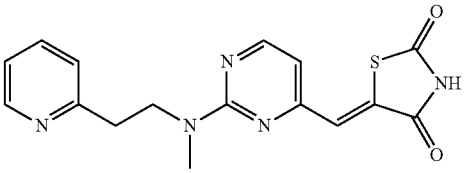
(Z)-5-((2-(4-(benzo[d][1,3]dioxol-5-ylmethyl)piperazin-1-yl)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione was prepared using the general displacement procedure and 1-(benzo[d][1,3]dioxol-5-ylmethyl)piperazine (16.6 mg, 37.4 mg theoretical, 44.3%). LC-MS m/z 426.5 (M+1).

Example 9



(Z)-5-((2-(4-(p-tolyl)piperazin-1-yl)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione was prepared using the general displacement procedure and 1-(p-tolyl)piperazine (12.5 mg, 33.6 mg theoretical, 37.2%). LC-MS m/z 382.5 (M+1).

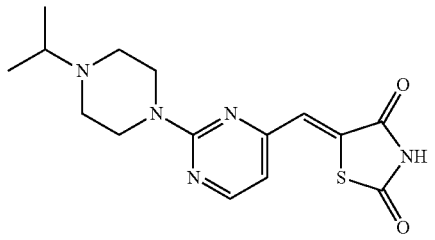
Example 10



(Z)-5-β2-(methyl(2-(pyridin-2-yl)ethyl)amino)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione was prepared using the general displacement procedure and N-methyl-2-

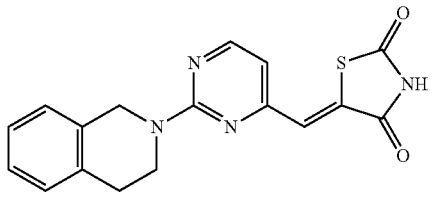
(pyridin-2-yl)ethanamine (13.7 mg, 30 mg theoretical, 45.6%). LC-MS m/z 342.4 (M+1).

Example 11



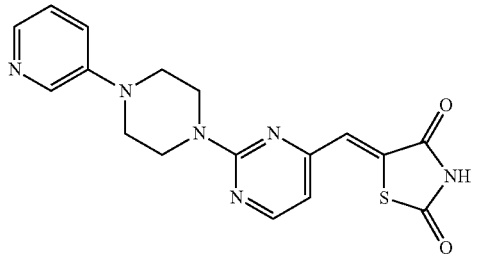
(Z)-5-((2-(4-isopropylpiperazin-1-yl)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione was prepared using the general displacement procedure and 1-isopropylpiperazine (15.3 mg, 29.3 mg theoretical, 52.1%). LC-MS m/z 334.4 (M+1).

Example 12



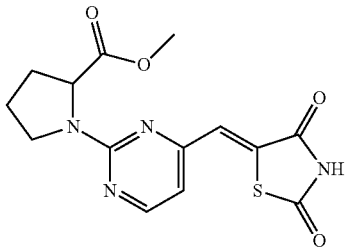
(Z)-5-((2-(3,4-dihydroisoquinolin-2(1H)-yl)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione was prepared using the general displacement procedure and 1,2,3,4-tetrahydroisoquinoline (0.1 mg, 29.8 mg theoretical, 0.3%). LC-MS m/z 339.4 (M+1).

Example 13



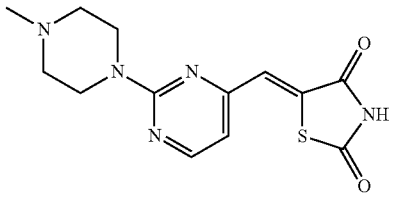
(Z)-5-((2-(4-(pyridin-2-yl)piperazin-1-yl)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione was prepared using the general displacement procedure and 1-(pyridin-2-yl)piperazine (25.7 mg, 32.4 mg theoretical, 79.3%). LC-MS m/z 369.4 (M+1).

Example 14



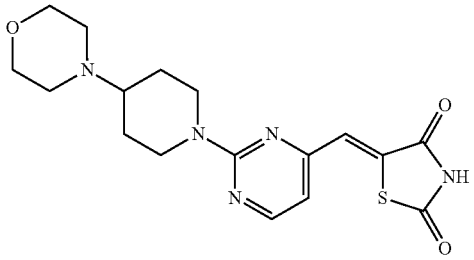
(Z)-methyl 1-(4-((2,4-dioxothiazolidin-5-ylidene)methyl)pyrimidin-2-yl)pyrrolidine-2-carboxylate was prepared using the general displacement procedure and methylpyrrolidine-2-carboxylate (3.1 mg, 29.4 mg theoretical, 10.5%). LC-MS m/z 335.4 (M+1).

Example 15



(Z)-5-β2-(4-methylpiperazin-1-yl)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione was prepared using the general displacement procedure and 1-methylpiperazine (0.1 mg, 26.9 mg theoretical, 0.4%). LC-MS m/z 306.4 (M+1).

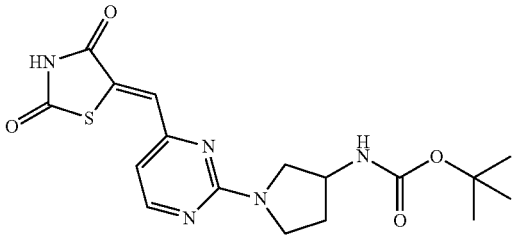
Example 16



(Z)-5-((2-(4-morpholinopiperidin-1-yl)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione was prepared using the

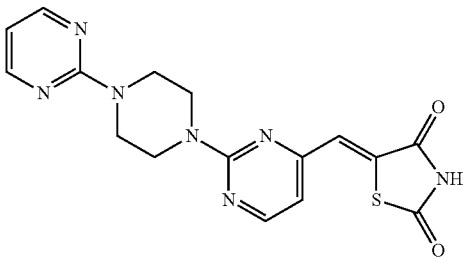
general displacement procedure and 4-(piperidin-4-yl)morpholine (14.7 mg, 33 mg theoretical, 44.5%). LC-MS m/z 376.4 (M+1).

Example 17



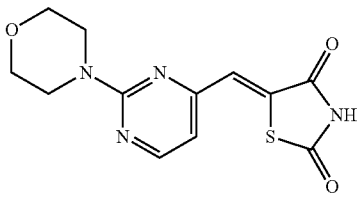
(Z)-tert-butyl (1-(4-((2,4-dioxothiazolidin-5-ylidene)methyl)pyrimidin-2-yl)pyrrolidin-3-yl)carbamate was prepared using the general displacement procedure and tert-butyl pyrrolidin-3-ylcarbamate (0.1 mg, 34.4 mg theoretical, 0.3%). LC-MS m/z 392.4 (M+1).

Example 18



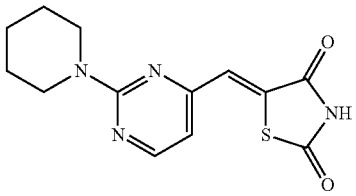
(Z)-5-((2-(4-(pyrimidin-2-yl)piperazin-1-yl)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione was prepared using the general displacement procedure and 2-(piperazin-1-yl)pyrimidine (3.1 mg, 32.5 mg theoretical, 9.5%). LC-MS m/z 370.4 (M+1).

Example 19



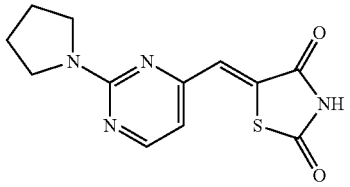
(Z)-5-((2-morpholinopyrimidin-4-yl)methylene)thiazolidine-2,4-dione was prepared using the general displacement procedure and morpholine (7.8 mg, 25.7 mg theoretical, 30.3%). LC-MS m/z 293.3 (M+1).

Example 20



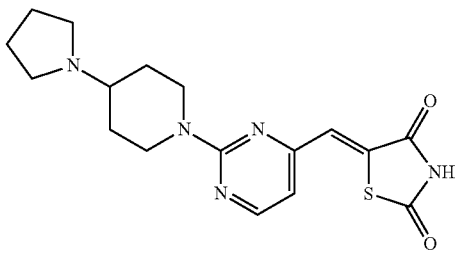
(Z)-5-((2-(piperidin-1-yl)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione was prepared using the general displacement procedure and piperidine (8.9 mg, 25.5 mg theoretical, 34.8%). LC-MS m/z 291.3 (M+1).

Example 21



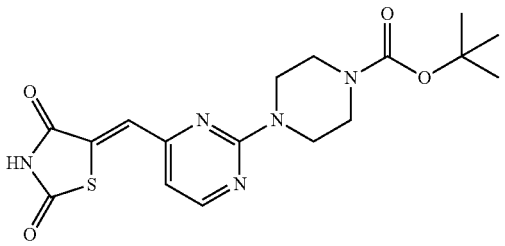
(Z)-5-((2-(pyrrolidin-1-yl)pyrimidin-4-yl)methylene) thiazolidine-2,4-dione was prepared using the general displacement procedure and pyrrolidine (8.3 mg, 24.3 mg theoretical, 34.1%). LC-MS m/z 277.3 (M+1).

Example 22



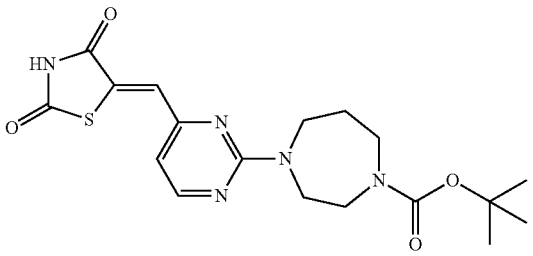
(Z)-5-((2-(4-(pyrrolidin-1-yl)piperidin-1-yl)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione was prepared using the general displacement procedure and 4-(pyrrolidin-1-yl)piperidine (9.3 mg, 31.6 mg theoretical, 29.4%). LC-MS m/z 360.4 (M+1).

Example 23



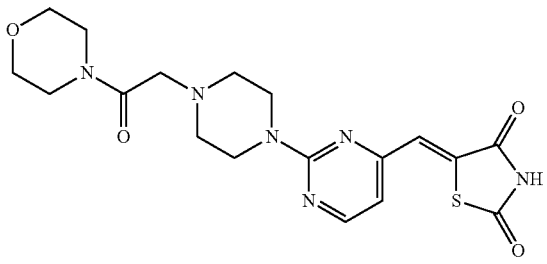
(Z)-tert-butyl 4-(4-((2,4-dioxothiazolidin-5-ylidene)methyl)pyrimidin-2-yl)piperazine-1-carboxylate was prepared using the general displacement procedure and tert-butyl piperazine-1-carboxylate (6.7 mg, 34.4 mg theoretical, 19.5%). LC-MS m/z 392.4 (M+1).

Example 24



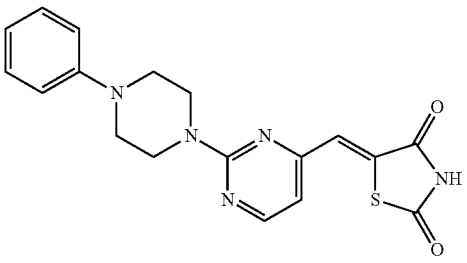
(Z)-tert-butyl 4-(4-((2,4-dioxothiazolidin-5-ylidene)methyl)pyrimidin-2-yl)-1,4-diazepane-1-carboxylate was prepared using the general displacement procedure and tert-butyl 1,4-diazepane-1-carboxylate (5.1 mg, 35.7 mg theoretical, 14.3%). LC-MS m/z 406.5 (M+1).

Example 25



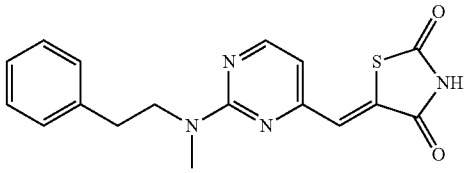
(Z)-5-((2-(4-(2-morpholino-2-oxoethyl)piperazin-1-yl)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione was prepared using the general displacement procedure and 1-morpholino-2-(piperazin-1-yl)ethanone (11.4 mg, 36.8 mg theoretical, 31%). LC-MS m/z 419.5 (M+1).

Example 26



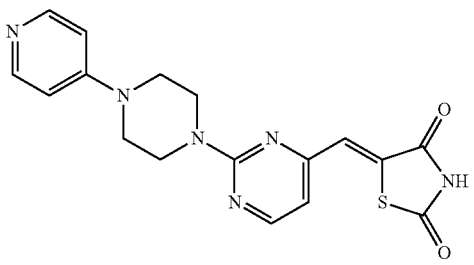
(Z)-5-((2-(4-phenylpiperazin-1-yl)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione was prepared using the general displacement procedure and 1-phenylpiperazine (11.3 mg, 32.3 mg theoretical, 35%). LC-MS m/z 368.4 (M+1).

Example 27



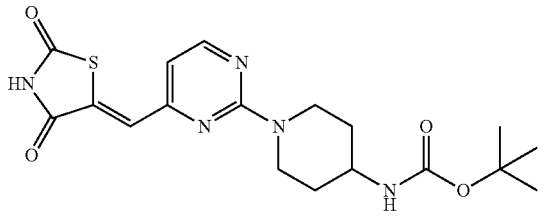
(Z)-5-((2-(methyl(phenethyl)amino)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione was prepared using the general displacement procedure and N-methyl-2-phenylethanamine (8.3 mg, 30 mg theoretical, 27.7%). LC-MS m/z 341.4 (M+1).

Example 28



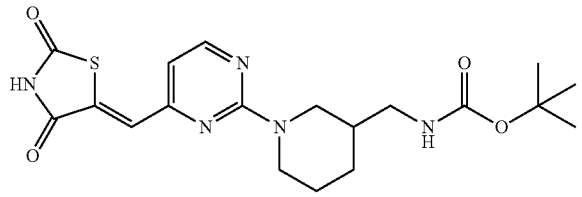
(Z)-5-((2-(4-(pyridin-4-yl)piperazin-1-yl)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione was prepared using the general displacement procedure and 1-(pyridin-4-yl)piperazine (7 mg, 32.4 mg theoretical, 21.6%). LC-MS m/z 369.4 (M+1).

Example 29



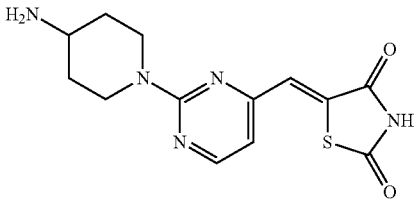
(Z)-tert-butyl (1-(4-((2,4-dioxothiazolidin-5-ylidene)methyl)pyrimidin-2-yl)piperidin-4-yl)carbamate was prepared using the general displacement procedure and tert-butyl piperidin-4-ylcarbamate (5.9 mg, 35.7 mg theoretical, 16.5%). LC-MS m/z 406.5 (M+1).

Example 30



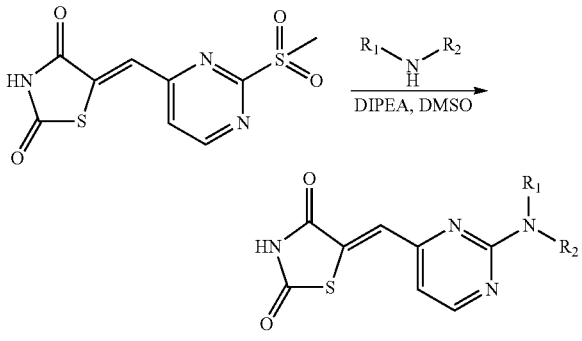
(Z)-tert-butyl ((1-(4-((2,4-dioxothiazolidin-5-ylidene)methyl)pyrimidin-2-yl)piperidin-3-yl)methyl)carbamate was prepared using the general displacement procedure and tert-butyl (piperidin-3-ylmethyl)carbamate (0.1 mg, 36.9 mg theoretical, 0.3%). LC-MS m/z 420.5 (M+1).

Example 31



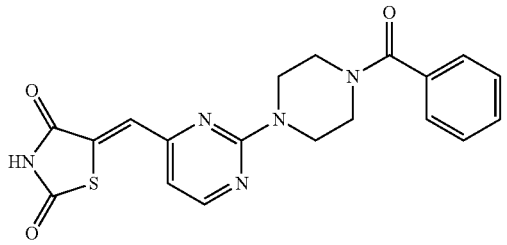
(Z)-5-((2-(4-aminopiperidin-1-yl)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione was prepared using the general displacement procedure and tert-butyl piperidin-4-ylcarbamate. The purified boc-protected was then treated with dichloromethane (1.0 mL), hydrochloric acid in methanol (500 μL, 1.25 M)) and shaken at 50° C. for 16 h. The reaction mixture was then concentrated under reduced pressure (Genevac HT-4) to provide (1.7 mg, 26.9 mg theoretical, 6.3%). LC-MS m/z 306.4 (M+1).

Example 32



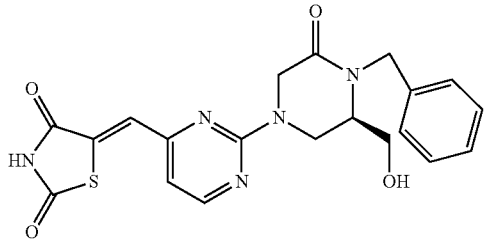
General displacement procedure 2: 2 dram round-bottomed vials were charged with (Z)-5-((2-(methylsulfonyl)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione (25 mg, 0.0877 mmol), DMSO (1 mL, 0.08 M), diisopropylethylamine (50 μL, 0.288 mmol, 3.2 equiv.), and the appropriate amine (0.0877 mmol, 1.0 equiv.). The reaction mixture was heated to 110° C. and shaken for 24 h. The solvent was removed under reduced pressure (Genevac HT-4) and the crude residues were purified using reverse phase HPLC (MS-triggered fraction collection) with an acetonitrile/water gradient and trifluoroacetic acid as a modifier. The pure fractions were then concentrated under reduced pressure (Genevac HT-4).

Example 33



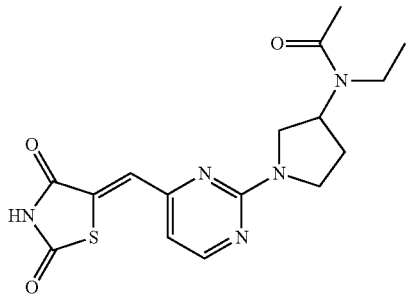
(Z)-5-((2-(4-benzoylpiperazin-1-yl)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione was prepared using the general displacement procedure and phenyl(piperazin-1-yl)methanone (4.1 mg, 34.7 mg theoretical, 11.8%). LC-MS m/z 396 (M+1).

Example 34



(R,Z)-5-((2-(4-benzyl-3-(hydroxymethyl)-5-oxopiperazin-1-yl)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione was prepared using the general displacement procedure and (R)-1-benzyl-6-(hydroxymethyl)piperazin-2-one (5.1 mg, 37.4 mg theoretical, 13.6%). LC-MS m/z 426 (M+1).

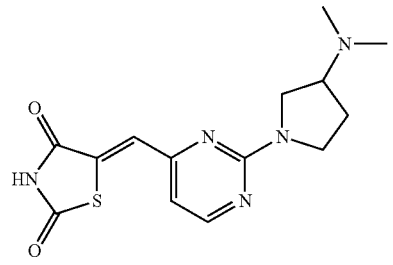
Example 35



(Z)-N-(1-(4-((2,4-dioxothiazolidin-5-ylidene)methyl)pyrimidin-2-yl)pyrrolidin-3-yl)-N-ethylacetamide was pre-

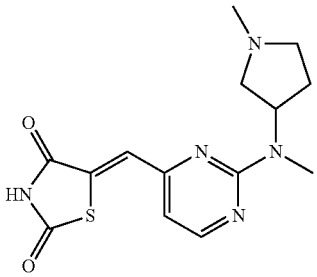
pared using the general displacement procedure and N-ethyl-N-(pyrrolidin-3-yl)acetamide (12.1 mg, 31.8 mg theoretical, 38%). LC-MS m/z 362 (M+1).

Example 36



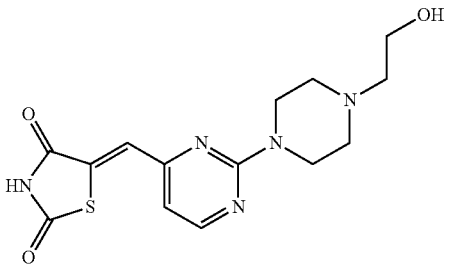
(Z)-5-((2-(3-(dimethylamino)pyrrolidin-1-yl)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione was prepared using the general displacement procedure and N,N-dimethylpyrrolidin-3-amine (12.2 mg, 28.1 mg theoretical, 43.4%). LC-MS m/z 320 (M+1).

Example 37



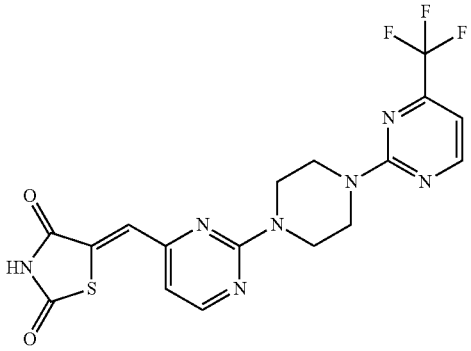
(Z)-5-((2-(methyl(1-methylpyrrolidin-3-yl)amino)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione was prepared using the general displacement procedure and N,1-dimethylpyrrolidin-3-amine (1.1 mg, 28.1 mg theoretical, 3.9%). LC-MS m/z 320 (M+1).

Example 38



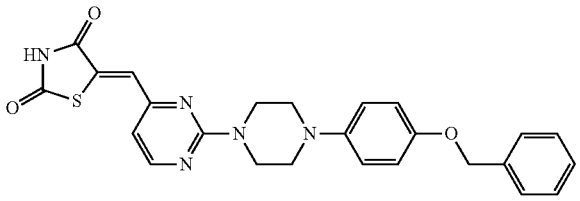
(Z)-5-((2-(4-(2-hydroxyethyl)piperazin-1-yl)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione was prepared using the general displacement procedure and 2-(piperazin-1-yl)ethanol (4.4 mg, 29.5 mg theoretical, 14.9%). LC-MS m/z 336 (M+1).

Example 39



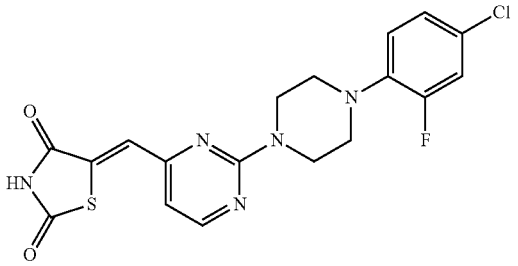
(Z)-5-((2-(4-(4-(trifluoromethyl)pyrimidin-2-yl)piperazin-1-yl)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione was prepared using the general displacement procedure and 2-(piperazin-1-yl)-4-(trifluoromethyl)pyrimidine (5.8 mg, 38.5 mg theoretical, 15.1%). LC-MS m/z 438 (M+1).

Example 40



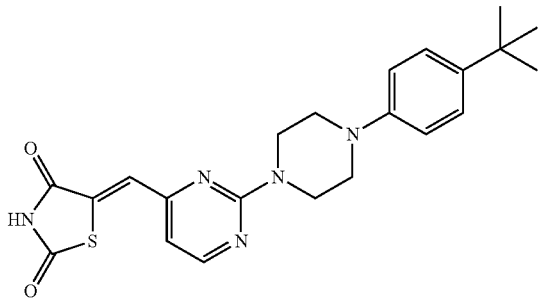
(Z)-5-((2-(4-(4-(benzyloxy)phenyl)piperazin-1-yl)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione was prepared using the general displacement procedure and 1-(4-(benzyloxy)phenyl)piperazine (4 mg, 41.7 mg theoretical, 9.6%). LC-MS m/z 474 (M+1).

Example 41



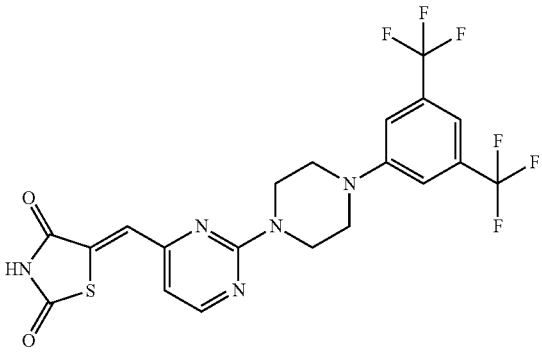
(Z)-5-((2-(4-(4-chloro-2-fluorophenyl)piperazin-1-yl)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione was prepared using the general displacement procedure and 1-(4-chloro-2-fluorophenyl)piperazine (4.8 mg, 36.9 mg theoretical, 13%). LC-MS m/z 420 (M+1).

Example 42



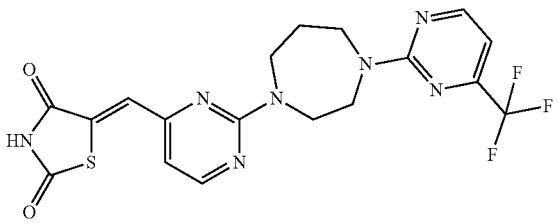
(Z)-5-((2-(4-(4-(tert-butyl)phenyl)piperazin-1-yl)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione was prepared using the general displacement procedure and 1-(4-(tert-butyl)phenyl)piperazine (3.7 mg, 37.2 mg theoretical, 10%). LC-MS m/z 424 (M+1).

Example 43



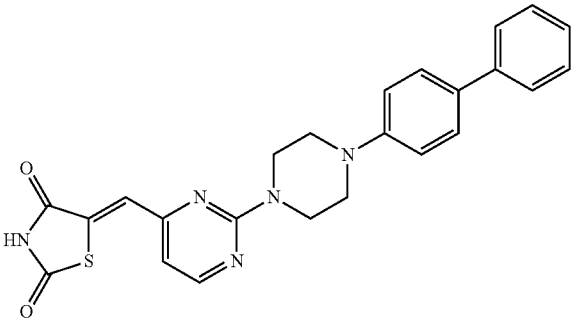
(Z)-5-((2-(4-(3,5-bis(trifluoromethyl)phenyl)piperazin-1-yl)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione was prepared using the general displacement procedure and 1-(3,5-bis(trifluoromethyl)phenyl)piperazine (3.8 mg, 44.3 mg theoretical, 8.6%). LC-MS m/z 504 (M+1).

Example 44



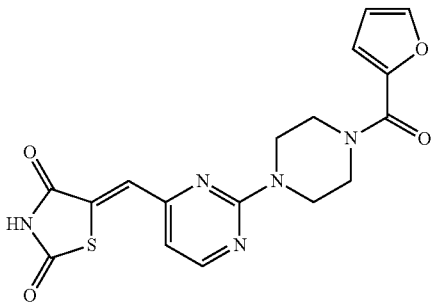
(Z)-5-((2-(4-(4-(trifluoromethyl)pyrimidin-2-yl)-1,4-diazepan-1-yl)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione was prepared using the general displacement procedure and 1-(4-(trifluoromethyl)pyrimidin-2-yl)-1,4-diazepane (4.9 mg, 39.7 mg theoretical, 12.3%). LC-MS m/z 452 (M+1).

Example 45



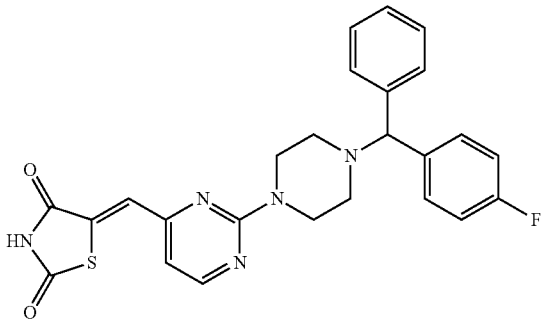
(Z)-5-((2-(4-([1,1'-biphenyl]-4-yl)piperazin-1-yl)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione was prepared using the general displacement procedure and 1-([1,1'-biphenyl]-4-yl)piperazine (1.2 mg, 39 mg theoretical, 3.1%). LC-MS m/z 444 (M+1).

Example 46



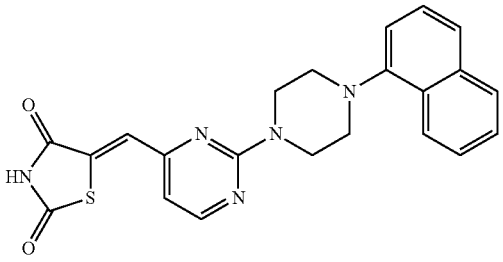
(Z)-5-((2-(4-(furan-2-carbonyl)piperazin-1-yl)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione was prepared using the general displacement procedure and furan-2-yl(piperazin-1-yl)methanone (6 mg, 33.9 mg theoretical, 17.7%). LC-MS m/z 386 (M+1).

Example 47



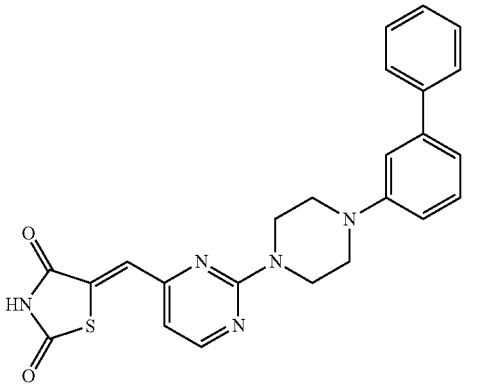
(Z)-5-((2-(4-((4-fluorophenyl)(phenyl)methyl)piperazin-1-yl)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione was prepared using the general displacement procedure and 1-((4-fluorophenyl)(phenyl)methyl)piperazine (14.4 mg, 41.8 mg theoretical, 34.4%). LC-MS m/z 476 (M+1).

Example 48



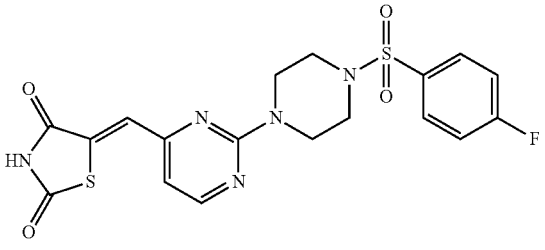
(Z)-5-((2-(4-(naphthalen-1-yl)piperazin-1-yl)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione was prepared using the general displacement procedure and 1-(naphthalen-1-yl) piperazine (6.2 mg, 36.7 mg theoretical, 16.9%). LC-MS m/z 418 (M+1).

Example 49



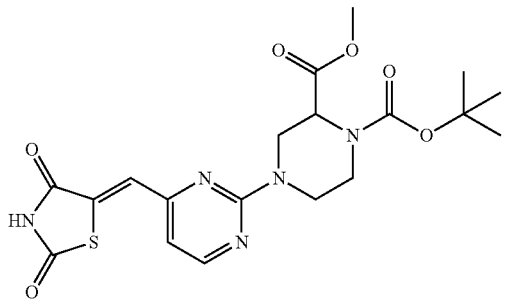
(Z)-5-((2-(4-([1,1'-biphenyl]-3-yl)piperazin-1-yl)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione was prepared using the general displacement procedure and 1-([1,1'-biphenyl]-3-yl)piperazine (10.4 mg, 39 mg theoretical, 26.7%). LC-MS m/z 444 (M+1).

Example 50



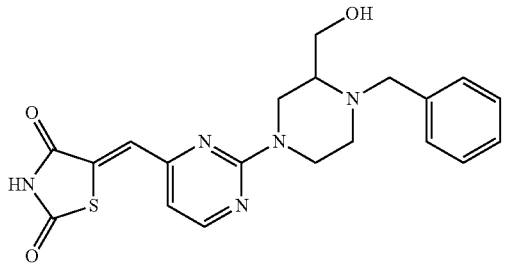
(Z)-5-((2-(4-((4-fluorophenyl)sulfonyl)piperazin-1-yl)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione was prepared using the general displacement procedure and 1-((4-fluorophenyl)sulfonyl)piperazine (5.2 mg, 39.6 mg theoretical, 13.1%). LC-MS m/z 450 (M+1).

Example 51



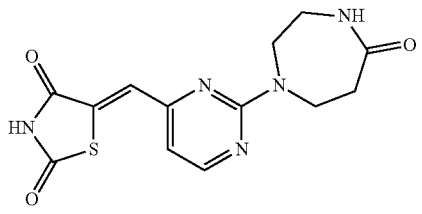
(Z)-1-tert-butyl 2-methyl 4-(4-((2,4-dioxothiazolidin-5-ylidene)methyl)pyrimidin-2-yl)piperazine-1,2-dicarboxylate was prepared using the general displacement procedure and 1-tert-butyl 2-methyl piperazine-1,2-dicarboxylate (2.8 mg, 39.6 mg theoretical, 7%). LC-MS m/z 450 (M+1).

Example 52



(Z)-5-((2-(4-benzyl-3-(hydroxymethyl)piperazin-1-yl) pyrimidin-4-yl)methylene)thiazolidine-2,4-dione was prepared using the general displacement procedure and (1-benzylpiperazin-2-yl)methanol (1.7 mg, 36.2 mg theoretical, 4.7%). LC-MS m/z 413 (M+1).

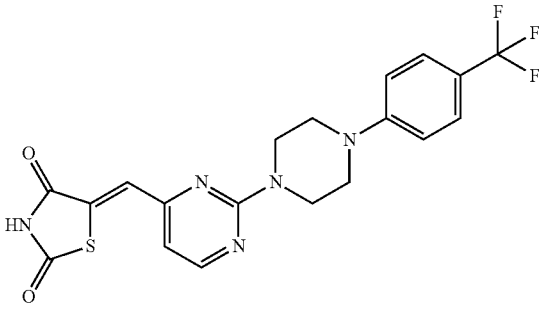
Example 53



(Z)-5-((2-(5-oxo-1,4-diazepan-1-yl)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione was prepared using the general

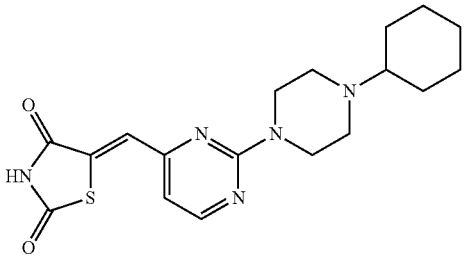
displacement procedure and 1,4-diazepan-5-one (1.1 mg, 28.1 mg theoretical, 3.9%). LC-MS m/z 320 (M+1).

Example 54



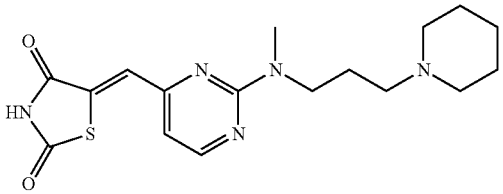
(Z)-5-((2-(4-(4-(trifluoromethyl)phenyl)piperazin-1-yl) pyrimidin-4-yl)methylene)thiazolidine-2,4-dione was prepared using the general displacement procedure and 1-(4-(trifluoromethyl)phenyl)piperazine (3.3 mg, 38.3 mg theoretical, 8.6%). LC-MS m/z 436 (M+1).

Example 55



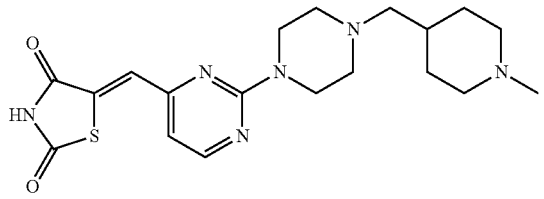
(Z)-5-((2-(4-cyclohexylpiperazin-1-yl)pyrimidin-4-yl) methylene)thiazolidine-2,4-dione was prepared using the general displacement procedure and 1-cyclohexylpiperazine (10.7 mg, 32.9 mg theoretical, 32.5%). LC-MS m/z 374 (M+1).

Example 56



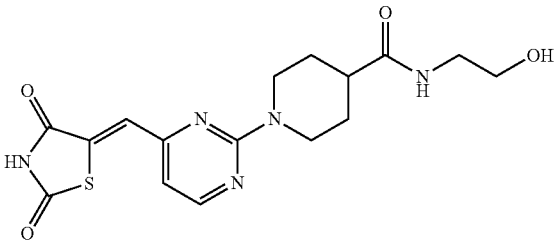
(Z)-5-((2-(methyl(3-(piperidin-1-yl)propyl)amino)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione was prepared using the general displacement procedure and N-methyl-3-(piperidin-1-yl)propan-1-amine (10.2 mg, 31.8 mg theoretical, 32.1%). LC-MS m/z 362 (M+1).

Example 57



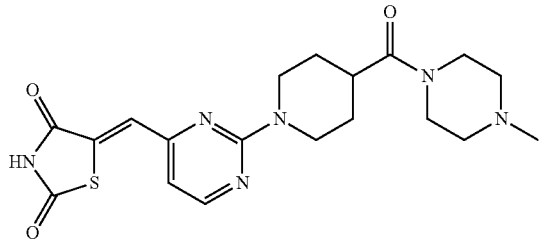
(Z)-5-((2-(4-((1-methylpiperidin-4-yl)methyl)piperazin-1-yl)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione was prepared using the general displacement procedure and 1-((1-methylpiperidin-4-yl)methyl)piperazine (7.3 mg, 42.3 mg theoretical, 17.2%). LC-MS m/z 403 (M+1).

Example 58



(Z)-1-(4-((2,4-dioxothiazolidin-5-ylidene)methyl)pyrimidin-2-yl)-N-(2-hydroxyethyl)piperidine-4-carboxamide was prepared using the general displacement procedure and N-(2-hydroxyethyl)piperidine-4-carboxamide (10.8 mg, 39.7 mg theoretical, 27.2%). LC-MS m/z 378 (M+1).

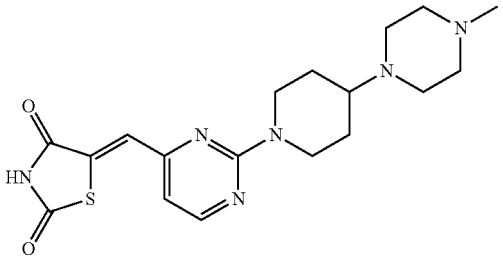
Example 59



(Z)-5-((2-(4-(4-methylpiperazine-1-carbonyl)piperidin-1-yl)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione was prepared using the general displacement procedure and

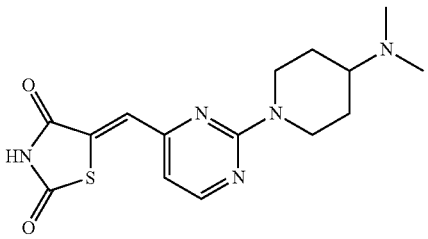
(4-methylpiperazin-1-yl)(piperidin-4-yl)methanone (5.5 mg, 43.8 mg theoretical, 12.6%). LC-MS m/z 417 (M+1).

Example 60



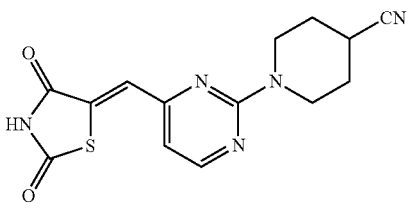
(Z)-5-((2-(4-(4-methylpiperazin-1-yl)piperidin-1-yl)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione was prepared using the general displacement procedure and 1-methyl-4-(piperidin-4-yl)piperazine (12.4 mg, 40.9 mg theoretical, 30.4%). LC-MS m/z 389 (M+1).

Example 61



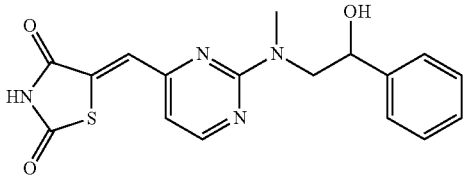
(Z)-5-((2-(4-(dimethylamino)piperidin-1-yl)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione was prepared using the general displacement procedure and N,N-dimethylpiperidin-4-amine (5 mg, 35.1 mg theoretical, 14.3%). LC-MS m/z 334 (M+1).

Example 62



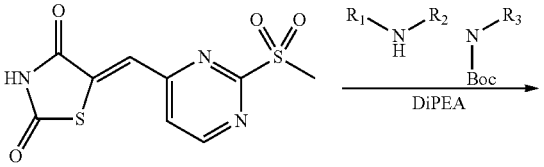
(Z)-1-(4-((2,4-dioxothiazolidin-5-ylidene)methyl)pyrimidin-2-yl)piperidine-4-carbonitrile was prepared using the general displacement procedure and piperidine-4-carbonitrile (7.5 mg, 33.2 mg theoretical, 22.6%). LC-MS m/z 316 (M+1).

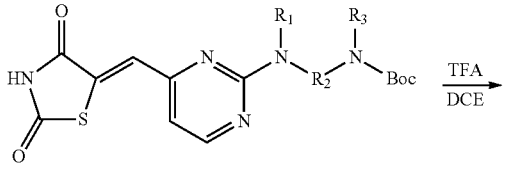
Example 63

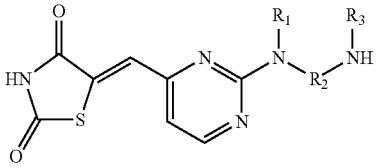


(Z)-5-((2-((2-hydroxy-2-phenylethyl)(methyl)amino)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione was prepared using the general displacement procedure and 2-(methylamino)-1-phenylethanol (10.8 mg, 37.5 mg theoretical, 28.8%). LC-MS m/z 357 (M+1).

Example 64

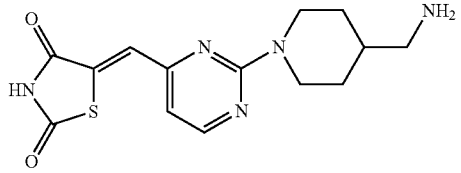






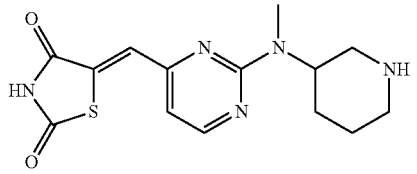
General displacement procedure 3: 2 dram round-bottomed vials were charged with (Z)-5-((2-(methylsulfonyl) pyrimidin-4-yl)methylene)thiazolidine-2,4-dione (50 mg, 0.175 mmol), DMSO (2 mL, 0.08 M), diisopropylethylamine (34 μL, 0.193 mmol, 1.1 equiv.), and the appropriate amine (0.175 mmol, 1.0 equiv.). The reaction mixture was heated to 100° C. and shaken for 24 h. The solvent was removed under reduced pressure (Genevac HT-4). The crude was then charged with 2 mL DCE and 500 μL of TFA and shaken for 24 h. The solvent was removed under reduced pressure (Genevac HT-4) and the crude residues were purified using reverse phase HPLC (MS-triggered fraction collection) with an acetonitrile/water gradient and trifluoroacetic acid as a modifier. The pure fractions were then concentrated under reduced pressure (Genevac HT-4).

Example 65



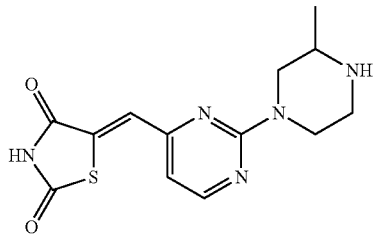
(Z)-5-((2-(4-(aminomethyl)piperidin-1-yl)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione was prepared using the general displacement procedure and tert-butyl (piperidin-4-ylmethyl)carbamate (49 mg, 55.9 mg theoretical, 88%). LC-MS m/z 320 (M+1).

Example 66



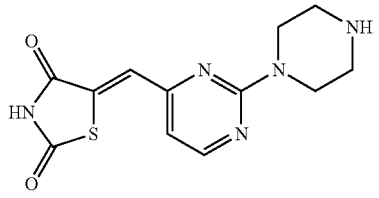
(Z)-5-((2-(methyl(piperidin-3-yl)amino)pyrimidin-4-yl) methylene)thiazolidine-2,4-dione was prepared using the general displacement procedure and tert-butyl 3-(methylamino)piperidine-1-carboxylate (2.3 mg, 55.9 mg theoretical, 4.1%). LC-MS m/z 320 (M+1).

Example 67



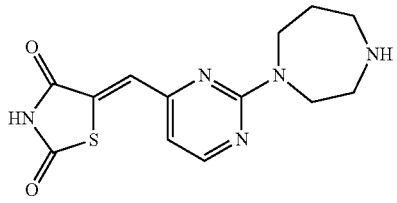
(Z)-5-((2-(3-methylpiperazin-1-yl)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione was prepared using the general displacement procedure and tert-butyl 2-methylpiperazine-1-carboxylate (1.5 mg, 53.4 mg theoretical, 2.8%). LC-MS m/z 306 (M+1).

Example 68



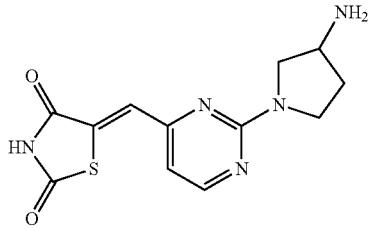
(Z)-5-((2-(piperazin-1-yl)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione was prepared using the general displacement procedure and tert-butyl piperazine-1-carboxylate (17.7 mg, 51 mg theoretical, 34.7%). LC-MS m/z 292 (M+1).

Example 69



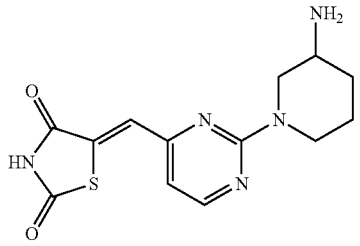
(Z)-5-((2-(1,4-diazepan-1-yl)pyrimidin-4-yl)methylene) thiazolidine-2,4-dione was prepared using the general displacement procedure and tert-butyl 1,4-diazepane-1-carboxylate (15.2 mg, 53.4 mg theoretical, 28.4%). LC-MS m/z 306 (M+1).

Example 70



(Z)-5-((2-(3-aminopyrrolidin-1-yl)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione was prepared using the general displacement procedure and tert-butyl pyrrolidin-3-ylcarbamate (16.5 mg, 51 mg theoretical, 32.4%). LC-MS m/z 292 (M+1).

Example 71

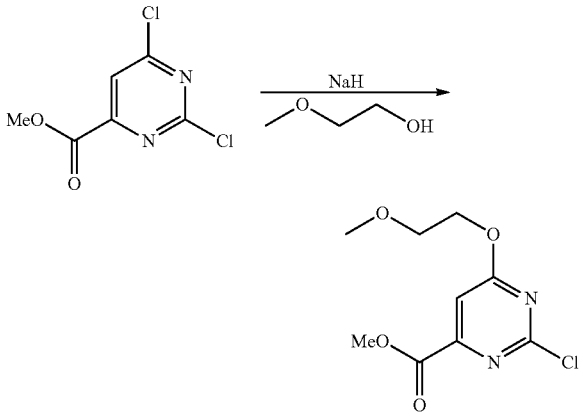


(Z)-5-((2-(3-aminopiperidin-1-yl)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione was prepared using the general

displacement procedure and tert-butyl piperidin-3-ylcarbamate (16.9 mg, 29.8 mg theoretical, 53.4%). LC-MS m/z 306 (M+1).

Example 72

Synthesis of (Z)-5-((6-(2-methoxyethoxy)-2-(4-(p-tolyl)piperazin-1-yl)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione

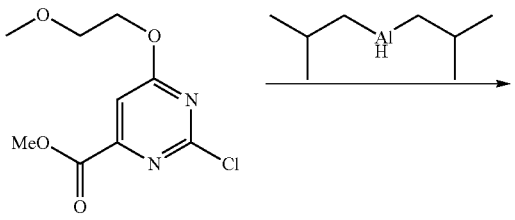


A 25 mL round-bottomed flask was charged with 2-methoxyethanol (57 μL, 1 equiv.) and THF (2.5 mL). 60% NaH in oil (21 mg, 1.1 equiv.) was added at 0° C. under argon. The reaction mixture was stirred for 5 min at −5° C. and for 1 h 15 min at RT. Methyl 2,6-dichloropyrimidine-4-carboxylate (150 mg, 1 equiv.) dissolved in THF (1 mL) was added over 5 min at −78° C. The reaction mixture was stirred for 4 h warming from −78° C. to 0° C. LC-MS after 3 h (−15° C.) showed 2 peaks (2:1 ratio) with the desired mass at 1.57 min and 1.67 min (M+1=247 & 249). The reaction mixture was quenched with 10% NH_4Cl (5 mL) at 0° C. The aqueous layer was extracted with EtOAc (3×10 mL). The combined organic layer was dried over Na_2SO_4 and concentrated under reduced pressure to provide 161 mg of a crude mixture of methyl 2-chloro-6-(2-methoxyethoxy)pyrimidine-4-carboxylate and methyl 6-chloro-2-(2-methoxyethoxy)pyrimidine-4-carboxylate which was partially separated by flash chromatography on silica gel (10 g, Hexanes/EtOAc 9:1 to 7:3).

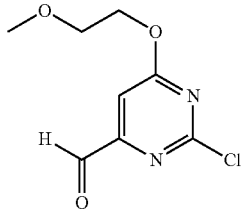
F1: 47 mg pure desired isomer 6-alkoxy (26%, 179 mg theoretical)

F2: 19.3 mg mixture of isomers (11%)

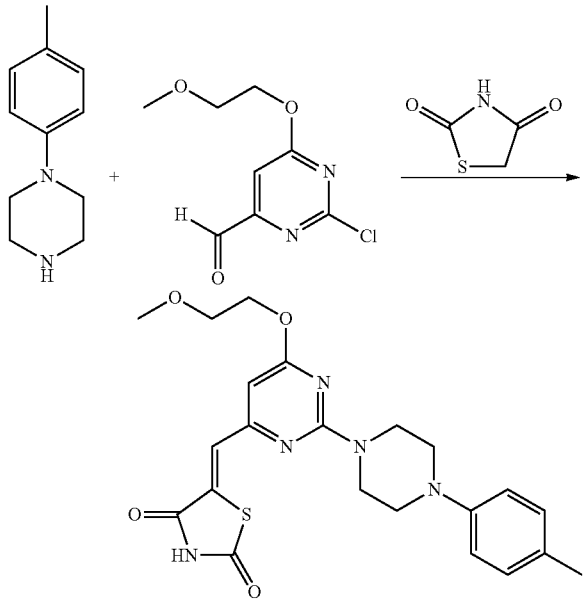
F3: 28.8 mg pure undesired isomer 2-alkoxy (16%)



-continued



A 25 mL round bottomed flask was charged with methyl 2-chloro-6-(2-methoxyethoxy)pyrimidine-4-carboxylate [SAD105-047F1] (45 mg, 1 equiv.) and CH_2Cl_2 (1 mL). 1 M DIBAL-H (0.2 mL, 1.1 equiv.) was added at −78° C. over 2 min under argon. The reaction mixture was stirred for 3 h at −78° C. but the LC-MS still showed a lot of starting material. Additional 1 M DIBAL-H (0.27 mL, 1.4 equiv.) was added at −78° C. over 2 min under argon and after 0.5 h LC-MS showed no more starting material but mostly 1 peak at 1.20 min (M+1=217, M+l+MeOH=249). The reaction mixture was quenched with MeOH (0.5 mL) and then with 10% NH_4Cl (1 mL). The reaction mixture was warmed to RT and then the solvent was concentrated under reduced pressure. The residue was diluted with 10% NH_4Cl (4 mL). The aqueous layer was extracted with EtOAc (3×10 mL). The combined organic layer was dried over Na_2SO_4 and concentrated under reduced pressure to provide 41.9 mg of the crude 2-chloro-6-(2-methoxyethoxy)pyrimidine-4-carbaldehyde as a yellow oil which was used in the next step without further purification, (H NMR δ: 9.91 (s, 1H); 7.23 (s, 1H); 4.59-4.64 (m, 2H), 3.7-3.8 (m, 2H); 3.44 (s, 3H).

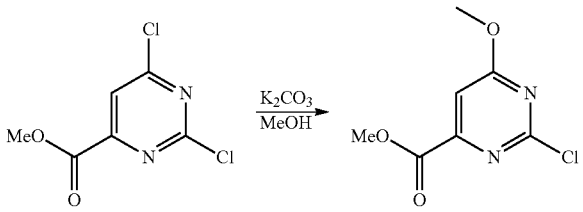


Crude 2-chloro-6-(2-methoxyethoxy)pyrimidine-4-carbaldehyde (sad105-052, 41.9 mg) was dissolved in ethanol (1.5 mL) and was added to a 10 mL vial containing the thiazolidine-dione (21.3 mg, 0.18 mmol) and the 1-(p-tolyl) piperazine (39.3 mg, 0.18 mmol). The reaction mixture was shaken at 80° C. for 15.5 h. LC-MS showed a peak with the desired mass at 2.18 min (M+1=456). The solvent was concentrated under reduced pressure and the residue was dissolved in EtOAc (20 mL) and washed with saturated

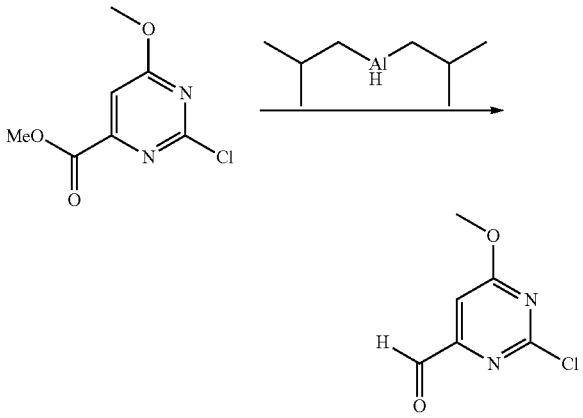
$NaHCO_3$ (10 mL). The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure to provide 85.7 mg of brown oil. Purification by flash chromatography (SiO_2,10 g, Hexanes/EtOAc 9:1 to 6:4 to 1:1) provided 11.5 mg (13.9% 2 steps, 83 mg theoretical) of pure (Z)-5-((6-(2-methoxyethoxy)-2-(4-(p-tolyl)piperazin-1-yl)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione as a yellow solid.

Example 73

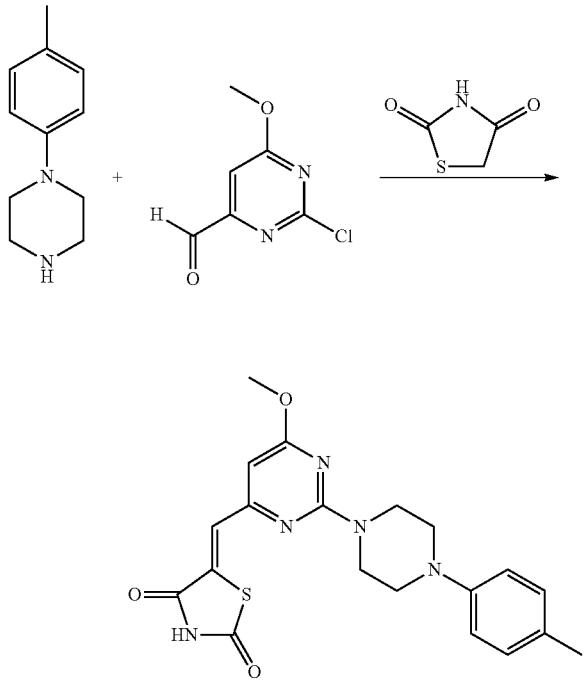
Synthesis of (Z)-5-((6-methoxy-2-(4-(p-tolyl)piperazin-1-yl)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione



A 40 mL round-bottomed vial was charged with methanol (120 μL of 200 μL MeOH in 1 mL Acetonitrile, 1 equiv.), K_2CO_3 (67 mg, 1 equiv.), methyl 2,6-dichloropyrimidine-4-carboxylate (100 mg, 1 equiv.), and acetonitrile (2 mL). The reaction mixture was shaken for 2.5 h at RT but LC-MS showed only starting material. The reaction mixture was then shaken for 1 h at 85° C. LC-MS showed the formation of a small amount of desired product (1.51 min, M+1=203). Methanol (0.200 mL, 10 equiv.) was added and the reaction mixture was shaken for 15 h at 85° C. LC-MS showed mostly 1 peak in the UV and MS at 1.53 min and a tiny amount of bis-methoxypyrimidine. The solid precipitate was filtered off and the filtrate was evaporated to give 89 mg (91% crude yield, theoretical 98 mg) of crude desired product. ^1H NMR showed an 11:1 mixture of desired product and bis-methoxypyrimidine side product (M+1=199). The material was used in the next step without further purification.



A 25 mL round-bottomed flask was charged with methyl 2-chloro-6-methoxypyrimidine-4-carboxylate [sad105-055 crude] (74 mg, 1 equiv.) under argon. 1M DIBAL-H in dichloromethane (0.73 mL, 2 equiv.) was added over 5 min and the reaction mixture was stirred at −78° C. for 45 min. After 0.5 h, LC-MS showed the reaction was complete. The reaction was quenched at −78° C. with methanol (0.5 mL) and then with 10% NH_4Cl (2 mL). The solvents were concentrated under reduced pressure and the residue was diluted with 10% NH_4Cl (3 mL). The aqueous layer was extracted with EtOAc (3×10 mL). The combined organic layer was dried over Na_2SO_4 and concentrated under reduced pressure to provide the crude product 2-chloro-6-methoxypyrimidine-4-carbaldehyde as an orange oil (76 mg, 63 mg theoretical, 121%). LC-MS m/z: 205.0: (M+1+MeOH, hemiacetal with methanol). Some over-reduced alcohol was also observed in the crude (2.17 min, M+1=175). The crude aldehyde was used directly in the next step without further purification.

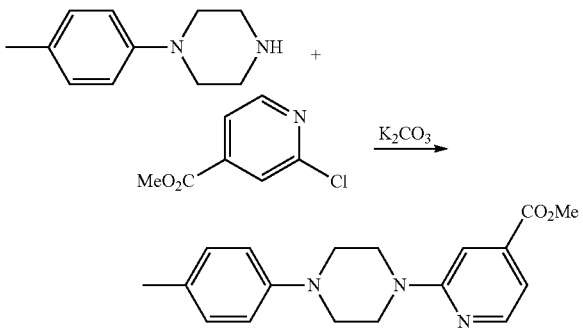


Crude 2-chloro-6-methoxypyrimidine-4-carbaldehyde (sad105-058, 76 mg) was dissolved in ethanol (2 mL) and was added to a 10 mL vial containing the thiazolidine-dione (42.8 mg, 0.37 mmol., 1 equiv.) and the 1-(p-tolyl)piperazine (70.8 mg, 0.40 mmol, 1.1 equiv.). The mixture was shaken for 45 h at 80° C. and for 15 h at 90° C. producing a precipitate. LC-MS of the solution showed some product at (M+1=412) and some intermediate at (M+1=430). The desired product crashed out of the solution and the LC-MS of the solution does not reflect well the conversion of the reaction. The yellow solid was filtered using a Pasteur pipette through a pad of glass wool and the solid was rinsed with EtOH (4×0.5 mL). The ethanol filtrate contains some desired product. The solid was re-dissolved in CH_2Cl_2 and the insoluble solid was filtered off. The filtrate was concentrated under reduced pressure to provide 20 mg of the desired product (Z)-5-((6-methoxy-2-(4-(p-tolyl)piperazin-1-yl)pyrimidin-4-yl)methylene) thiazolidine-2,4-dione (97.3% pure). The insoluble solid was partitioned between saturated $NaHCO_3$ (3 mL) and CH_2Cl_2 (2×5 mL). The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure to provide an additional

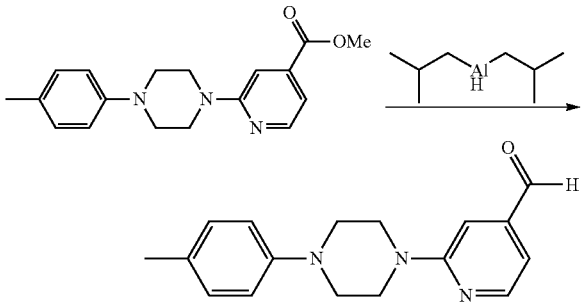
13.4 mg of the desired product (total 33.4 mg, 150 mg theoretical, 22%). LC-MS m/z: 412 (M+1).

Example 74

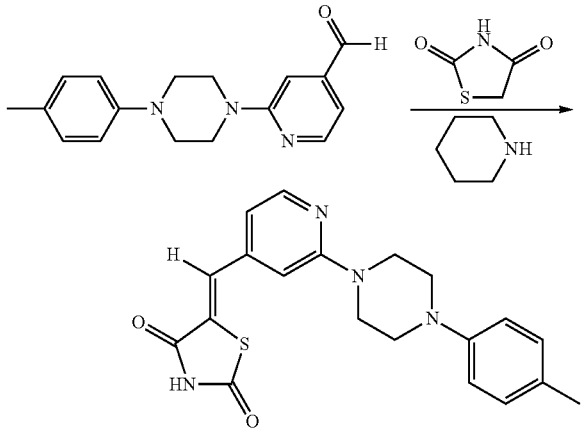
Synthesis of (Z)-5-((2-(4-(p-tolyl)piperazin-1-yl) pyridin-4-yl)methylene)thiazolidine-2,4-dione



A 40 mL round-bottomed vial was charged with methyl 2-chloroisonicotinate (200 mg, 1.17 mmol, 1 equiv.) and 1-(p-tolyl)piperazine (205 mg, 1.17 mmol, 1 equiv.). Toluene (3 mL) and DMSO (3 mL) were added followed by potassium carbonate (403 mg, 2.9 mmol, 2.5 equiv.). The mixture was shaken for 18 h at 100° C. LC-MS after 18 h showed a peak at 1.68 min with the desired mass (M+1=312) with the chloropyridine starting material co-eluting (M+1=172). The reaction mixture was diluted with water (5 mL) and the aqueous layer was extracted with CH_2Cl_2 (3×10 mL). The combined organic layer was dried over Na_2SO_4 and then concentrated under reduced pressure. The crude mixture was purified on silica gel (10 g, Hexanes/EtOAc 9:1 to 1:1) to provide the desired product as white crystals (27 mg, 67 mg theoretical, 40%).



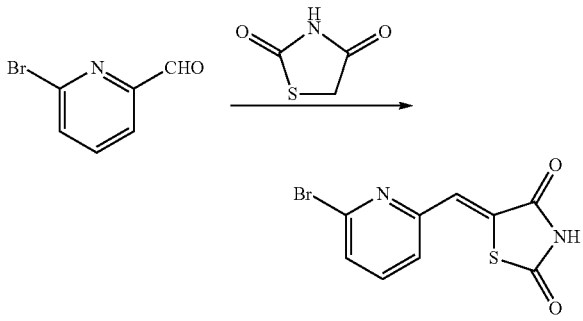
A 25 mL round-bottomed flask was charged with methyl 2-(4-(p-tolyl)piperazin-1-yl)isonicotinate (27 mg, 0.087 mmol, 1 equiv.) and CH_2Cl_2 (1 mL). 1 M DIBAL-H in CH_2Cl_2 (130 μL, 0.13 mmol, 1.5 equiv.) was added under argon at −78° C. over 2 min. The reaction mixture was quenched with MeOH (0.5 mL) at −78° C. The LC-MS of the crude mixture showed a 1:1 mixture of the alcohol (1.21 min, M+1=284) and the aldehyde as a hemiacetal with methanol (1.38 min, M+1+MeOH=314.3). The crude aldehyde was used directly in the next step without any further purification.



Crude 2-(4-(p-tolyl)piperazin-1-yl)isonicotinaldehyde [sad105-080] was dissolved in ethanol (1 mL) and was added to a 10 mL vial containing the thiazolidine-dione (10.2 mg, 0.087 mmol) and the 1-(p-tolyl)piperazine (5.9 mg, 0.087 mmol). The reaction mixture was shaken at 90° C. for 19.5 h. LC-MS showed a new peak with the desired mass at 1.78 min (M+1=381). The reaction was concentrated under reduced pressure and the residue was purified by flash chromatography (SiO_2,10 g, Hexanes/EtOAc 9:1 to 4:6) to provide 10.1 mg (30% over two steps, 33.1 mg theoretical) of (Z)-5-(2-(4-(p-tolyl)piperazin-1-yl)pyridin-4-yl)methylene)thiazolidine-2,4-dione as a yellow solid. The yellow solid was dissolved in hot EtOH (0.5 mL). On cooling a yellow solid precipitated, which was filtered through a pad of glass wool and washed with 0.25 mL ethanol. The solid was re-dissolved in CH_2Cl_2 and was concentrated under reduced pressure to provide 1.7 mg of the title product. LC-MS m/z: (M+1=381).

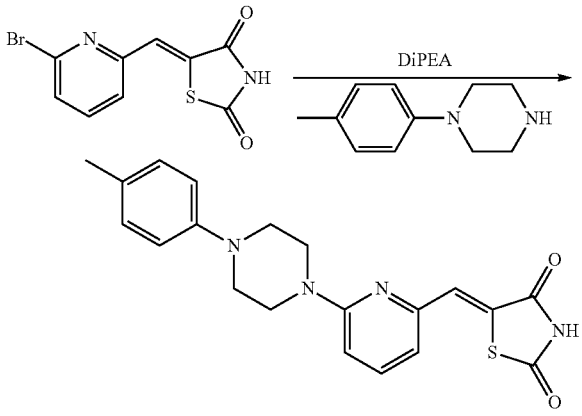
Example 75

Synthesis of (Z)-5-((6-(4-(p-tolyl)piperazin-1-yl) pyridin-2-yl)methylene)thiazolidine-2,4-dione



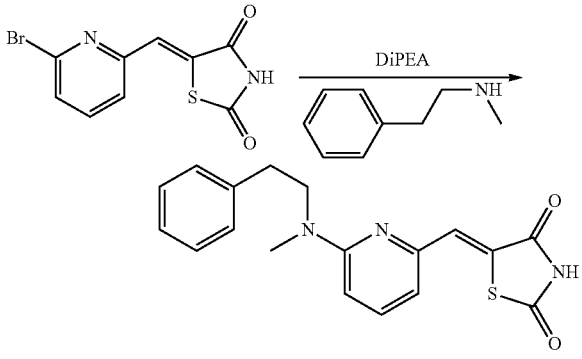
A 40 mL round-bottomed vial was charged with thiazolidine-2,4-dione (300 mg, 2.56 mmol, 1 equiv.) and 6-bromopicolinaldehyde (477 mg, 2.56 mmol, 1 equiv.). Toluene (5 mL, 0.5 M), glacial acetic acid (22 μL, 0.38 mmol, 0.15 equiv.), and piperidine (25 μL, 0.25 mmol, 0.1 equiv.) were added and the vial was purged with argon. The mixture was shaken for 16 h at 125° C. The resulting solid was collected by filtration and then washed with acetone (3×5 mL). The solid was dried under reduced pressure to provide (Z)-5-((6-bromopyridin-

2-yl)methylene)thiazolidine-2,4-dione (439 mg, 731 mg theoretical, 60%). LC-MS m/z: 286 (M+1).



An 8 mL round bottomed vial was charged with 1-(p-tolyl) piperazine (56 mg, 0.318 mmol, 1 equiv.) and DMSO (1 mL, 0.3 M), DiPEA (105 μL, 0.636 mmol, 2 equiv.), (Z)-5-((6-bromopyridin-2-yl)methylene)thiazolidine-2,4-dione (91 mg, 0.318 mmol, 1 equiv.), and the vial was purged with argon. The mixture was shaken for 48 h at 110° C. The reaction mixture was then partitioned between CH_2Cl_2 (10 mL) and sat. NaCl (20 mL). The aqueous layer was back extracted with CH_2Cl_2 (2×15 mL) and the combined organic layer was dried over xxx and concentrated under reduced pressure to provide an orange residue. The orange residue was triturated with ether (3×15 mL) to provide (Z)-5-((6-(4-(p-tolyl)piperazin-1-yl)pyridin-2-yl)methylene)thiazolidine-2,4-dione as an orange solid (65 mg, 122 mg theoretical, 53%). LC-MS m/z: 382 (M+1).

Example 76

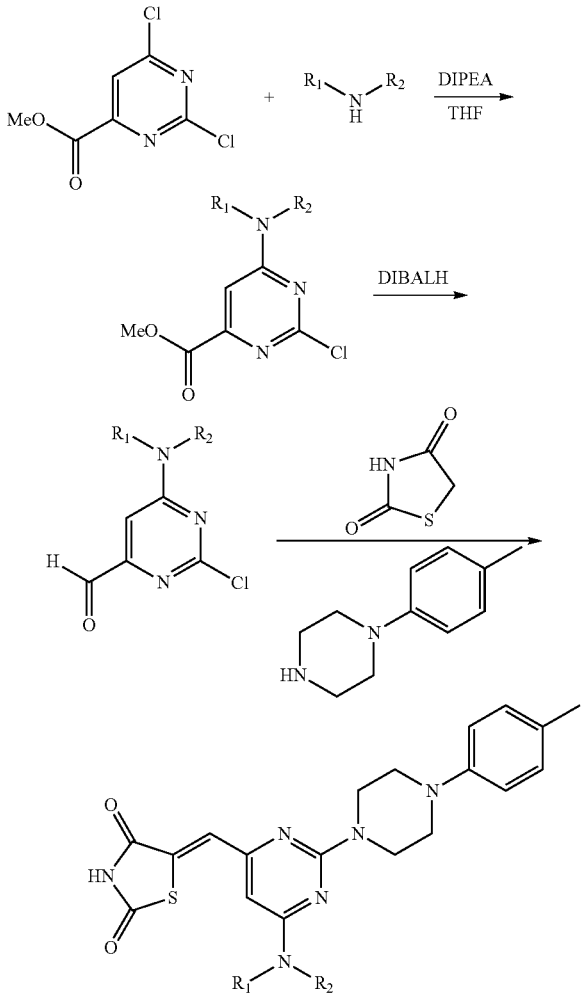


(Z)-5-((6-(methyl(phenethyl)amino)pyridin-2-yl) methylene)thiazolidine-2,4-dione

An 8 mL round-bottomed vial was charged with N-methyl-2-phenylethanamine (43 mg, 0.318 mmol, 1 equiv.) and DMSO (1 mL, 0.3 M), DiPEA (105 μL, 0.636 mmol, 2 equiv.), (Z)-5-((6-bromopyridin-2-yl)methylene)thiazolidine-2,4-dione (91 mg, 0.318 mmol, 1 equiv.), and the vial was purged with argon. The mixture was shaken for 48 h at 110° C. The reaction mixture was then partitioned between CH_2Cl_2 (10 mL) and sat. NaCl (20 mL). The aqueous layer was back extracted with CH_2Cl_2 (2×15 mL) and the combined organic layer was dried over xxx and concentrated under reduced pressure to provide an orange residue. The orange residue was triturated with ether (3×15 mL) to provide (Z)-5-((6-(methyl(phenethyl)amino)pyridin-2-yl)methylene) thiazolidine-2,4-dione as an orange film (2.6 mg, 175 mg theoretical, 5%). LC-MS m/z: 340 (M+1).

Example 77

General Procedure 1 for the Preparation of Amino-Analogs



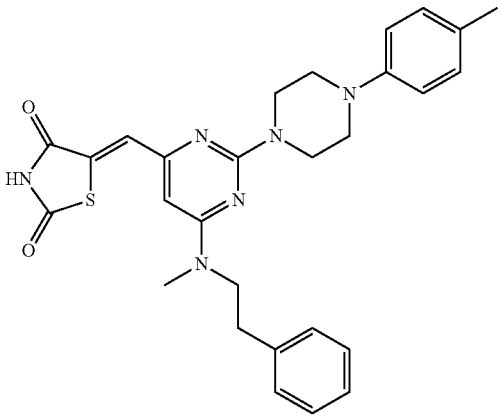
Methyl 2,6-dichloropyrimidine-4-carboxylate (200 mg, 0.966 mmol) in 2 mL of THF was treated with DIPEA (185 μL, 1.06 mmol) and the reaction was then cooled to 0° C. A solution of the appropriate amine (1 equiv., 0.966 mmol) in 2 mL of THF was then added slowly to the reaction mixture. The reaction mixture was shaken for 2 h and then concentrated under reduced pressure to provide a light yellow crude product, which was used without any further purification.

The light yellow crude product (1 equiv.) was treated with DCM (2 mL). The reaction mixture was then cooled to −70° C. and treated dropwise with 1 M DIBALH (180 μL, 1.1 equiv.) and stirred for 2 h. Another 100 μL of DIBALH was added dropwise and stirred for an additional 3 h. MeOH (1 mL) was then added to quench the reaction. The reaction

mixture was then allowed to warm to room temperature and partitioned between water (5 mL) and DCM (5 mL). The DCM layer was collected and concentrated under reduced pressure. Flash chromatography using 50%-80% EtOAc/Hexanes provided the desired aldehyde.

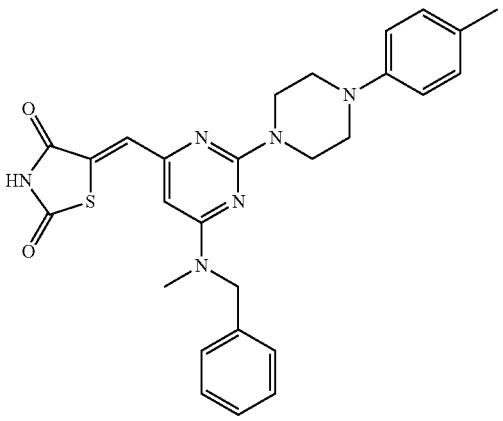
The aldehyde was treated with thiazolidine-2,4-dione (1 equiv.) and 1-(p-tolyl)piperazine (1.1 equiv.) in 2 mL of EtOH. The reaction mixture was then heated to 85° C. for 16 h and then further heated to 95° C. for 24 h. The reaction mixture was then concentrated and purified by Biotage chromatography using 1:1 hexanes/EtOAc to provide the final amino-analogs.

Example 78



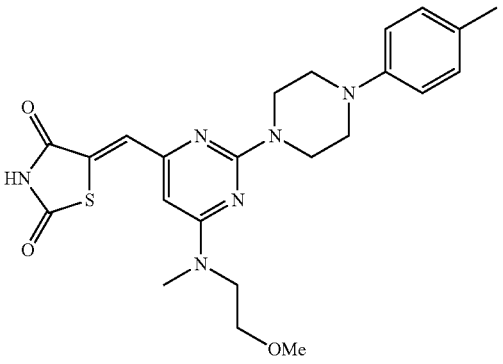
(Z)-5-((6-(methyl(phenethyl)amino)-2-(4-(p-tolyl)piperazin-1-yl)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione was prepared using General Procedure 1 for the Preparation of Amino-Analogs and N-methyl-2-phenylethanamine (4.2 mg, 90 mg theoretical, 5%, 3 steps). LC-MS m/z: 515 (M+1).

Example 79



(Z)-5-((6-(benzyl(methyl)amino)-2-(4-(p-tolyl)piperazin-1-yl)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione was prepared using General Procedure 1 for the Preparation of Amino-Analogs and N-methylbenzylamine (5.1 mg, 85 mg theoretical, 6%, 3 steps). LC-MS m/z: 501 (M+1).

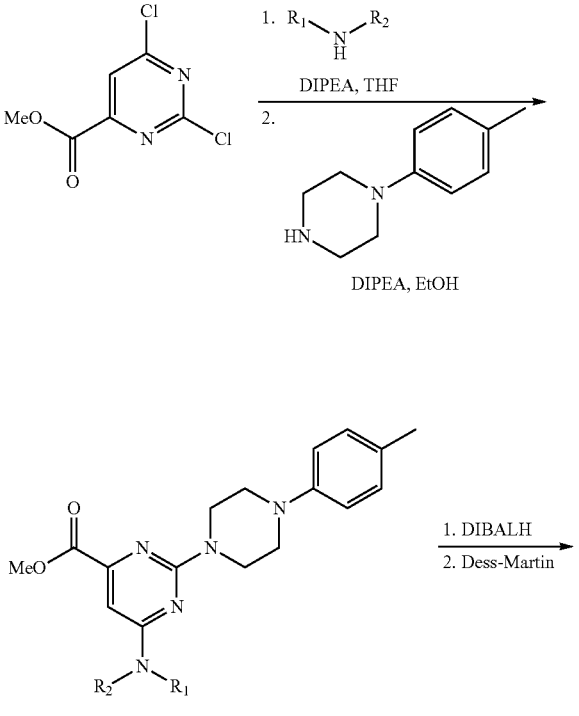
Example 80



(Z)-5-((6-((2-methoxyethyl)(methyl)amino)-2-(4-(p-tolyl)piperazin-1-yl)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione was prepared using the general displacement procedure and N-methyl-1-phenylmethanamine (34 mg, 142 mg theoretical, 23.9%, 3 steps). LC-MS m/z 501: (M+1).

Example 81

General Procedure 2 for the Preparation of Amino-Analogs



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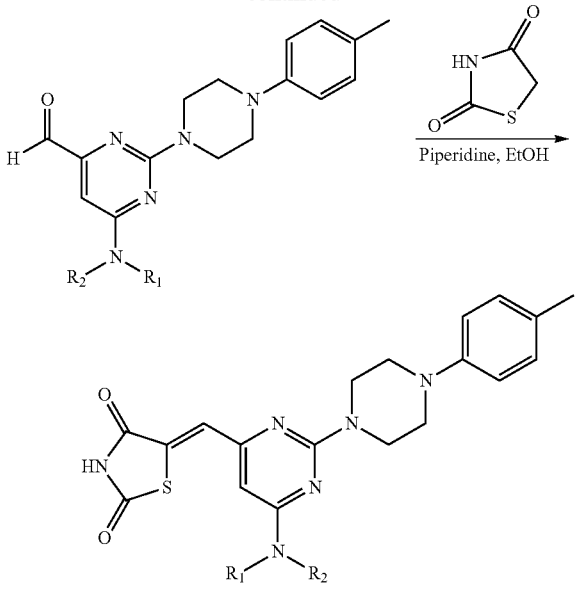


Methyl 2,6-dichloropyrimidine-4-carboxylate (200 mg, 0.966 mmol) in 2 mL of THF was treated with DIPEA (185 μL, 1.06 mmol) and then cooled to 0° C. A solution of the appropriate amine (1 equiv., 0.966 mmol) in 2 mL of THF was then added slowly. The reaction mixture was shaken for 2 h and concentrated under reduced pressure to provide a light yellow crude product, which was used without any further purification.

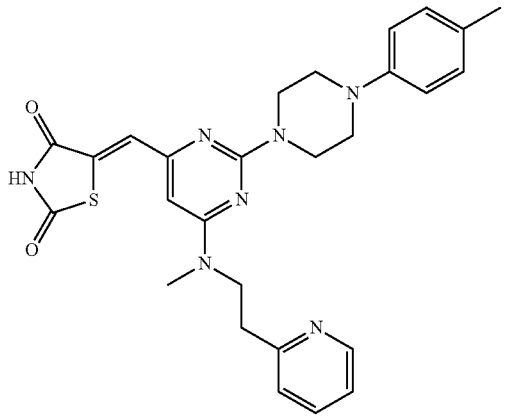
The crude material was treated with 2 mL of EtOH, DIPEA (1.1 equiv.), and 1-(p-tolyl)piperazine (1 equiv.). The reaction mixture was then heated to 90° C. for 2 d. LCMS showed the desired product along with the EtO version of the ester. The reaction mixture was then concentrated under reduced pressure and purified using a Biotage with 10-100% EtOAc/Hexanes to provide the desired di-aminoester intermediate.

The di-aminoester intermediate was treated with DCM (2 mL) and cooled to −10° C. DIBALH (3 equiv.) was added dropwise and the reaction mixture was allowed to warm to room temperature and stirred for 1 h. Methanol (1 mL) was added to quench the reaction and then allowed to stir for 30 min. The reaction mixture was then partitioned between DCM (10 mL) and H_2O (10 mL). The aqueous layer was back extracted with DCM (2×10 mL) and the combined organic layer was concentrated under reduced pressure. The crude residue was purified on silica gel using 5-10% MeOH/DCM to provide the desired alcohol.

The alcohol (1 equiv.) was treated with 2 mL of DCM and the reaction mixture was cooled to 0° C. and treated with 1.4 mL of 15% Dess Martin reagent in DCM. The reaction mixture was stirred for 1 h and treated with an additional portion of Dess Martin reagent (1.1 equiv.) at 0° C., and the reaction mixture was allowed to warm to room temperature and stirred for 1 h. The reaction mixture was then concentrated under reduced pressure and the crude residue was purified by flash chromatography using 5-10% MeOH/DCM to provide the desired aldehyde.

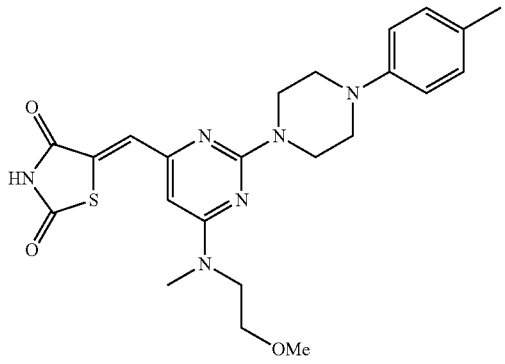
The aldehyde was treated with thiazolidine-2,4-dione (1 equiv.), piperidine (0.8 equiv.), and 2 mL of EtOH. The reaction mixture was then heated to 85° C. for 16 h and then concentrated under reduced pressure. The residue was then triturated with DCM (2 mL), MeOH (2 mL), and EtOAc (2 mL) to provide the final amino-analogs.

Example 82



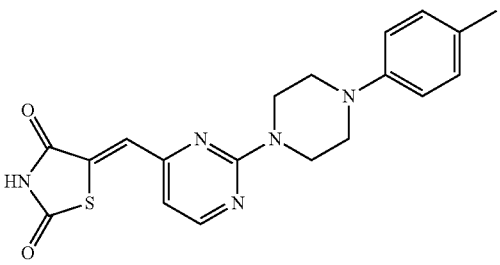
(Z)-5-((6-(methyl(2-(pyridin-2-yl)ethyl)amino)-2-(4-(p-tolyl)piperazin-1-yl)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione was prepared using the general displacement procedure and N-methyl-2-(pyridin-2-yl)ethanamine (12.7 mg, 160 mg theoretical, 1.7%, 5 steps). LC-MS m/z: 516 (M+1).

Example 83



(Z)-5-((6-((2-methoxyethyl)(methyl)amino)-2-(4-(p-tolyl)piperazin-1-yl)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione was prepared using the general displacement procedure and 2-methoxy-N-methylethanamine (34 mg, 680 mg theoretical, 5%, 5 steps). LC-MS m/z: 469 (M+1).

Example 84



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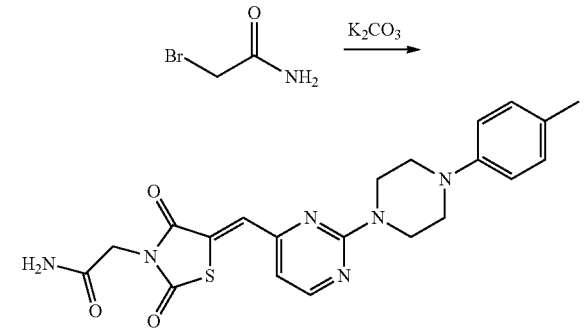
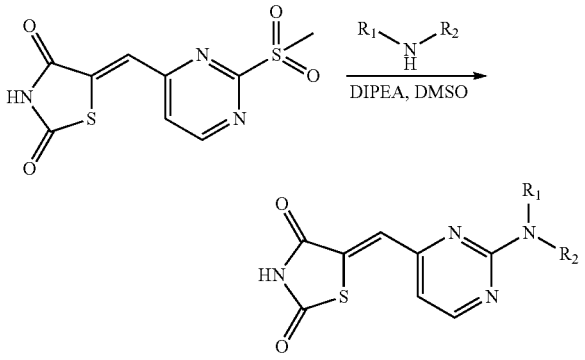


(Z)-2-(2,4-dioxo-5-((2-(4-(p-tolyl)piperazin-1-yl) pyrimidin-4-yl)methylene)thiazolidin-3-yl)acetamide

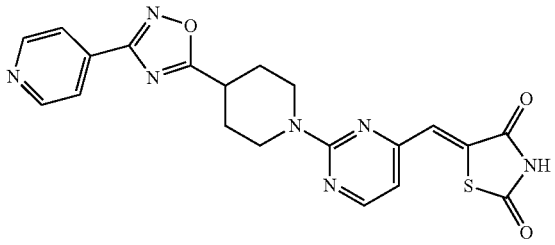
To 10 mg of (Z)-5-((2-(4-(p-tolyl)piperazin-1-yl)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione was added 4 mg of 2-bromoacetamide, 4 mg of potassium carbonate, and 0.5 mL of DMF. The reaction mixture was heated to 55° C. for 4 h, concentrated under reduced pressure, and purified using reverse phase HPLC (MS-triggered fraction collection) with an acetonitrile/water gradient using trifluoroacetic acid as a modifier. The pure fractions were then concentrated under reduced pressure (Genevac HT-4) to provide (Z)-2-(2,4-dioxo-5-((2-(4-(p-tolyl)piperazin-1-yl)pyrimidin-4-yl)methylene)thiazolidin-3-yl)acetamide (4 mg, 11.5 mg theoretical, 35%). LC-MS m/z: 439 (M+1).

Example 85



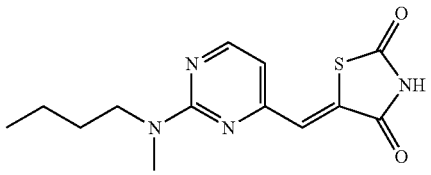
General Displacement Procedure:2 dram round-bottomed vials were charged with (Z)-5-((2-(methylsulfonyl)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione (25 mg, 0.0877 mmol) prepared according to the general procedure, DMSO (1 mL, 0.08 M), diisopropylethylamine (50 μL, 0.288 mmol, 3.2 equiv.), and the appropriate amine (0.0877 mmol, 1.0 equiv.). The reaction mixture was heated to 110° C. and shaken for 24 h. The solvent was removed under reduced pressure (Genevac HT-4) and the crude residues were purified using reverse phase HPLC (MS-triggered fraction collection) with an acetonitrile/water gradient and trifluoroacetic acid as a modifier. The pure fractions were then concentrated under reduced pressure (Genevac HT-4).

Example 86



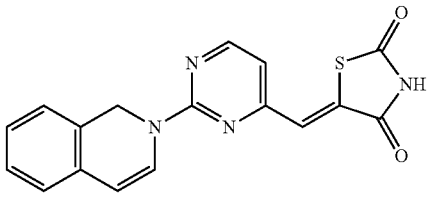
(Z)-5-((2-(4-(3-(pyridin-4-yl)-1,2,4-oxadiazol-5-yl)piperidin-1-yl)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione was prepared using the general displacement procedure and 5-(piperidin-4-yl)-3-(pyridin-4-yl)-1,2,4-oxadiazole (6 mg, 45.8 mg theoretical, 13%). LC-MS m/z 436.4 (M+1).

Example 87



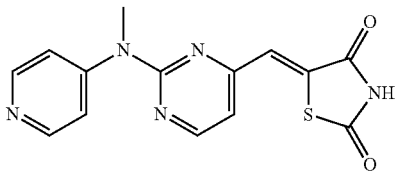
(Z)-5-((2-(butylmethyl)amino)pyrimidin-4-yl)methylene) thiazolidine-2,4-dione was prepared using the general displacement procedure and N-methylbutan-1-amine (12.5 mg, 30.7 mg theoretical, 40.7%). LC-MS m/z 293.3 (M+1).

Example 88



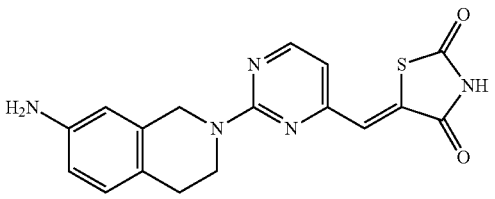
(Z)-5-((2-(isoquinolin-2(1H)-yl)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione was prepared using the general displacement procedure 1,2,3,4-tetrahydroisoquinoline (2 mg, 35 mg theoretical, 5.7%). LC-MS m/z 337.1 (M+1).

Example 89



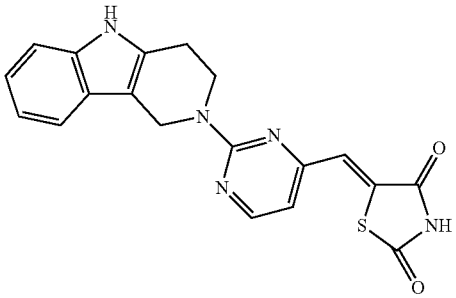
(Z)-5-((2-(methyl(pyridin-4-yl)amino)pyrimidin-4-yl) methylene)thiazolidine-2,4-dione was prepared using the general displacement procedure and N-methylpyridin-4-amine (11.7 mg, 32.9 mg theoretical, 35.5%). LC-MS m/z 314.3 (M+1).

Example 90



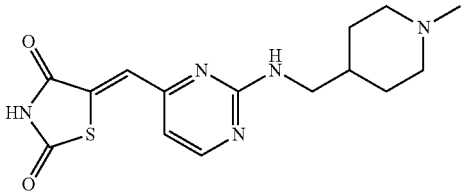
(Z)-5-((2-(7-amino-3,4-dihydroisoquinolin-2(1H)-yl)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione was prepared using the general displacement procedure and 1,2,3,4-tetrahydroisoquinolin-7-amine (12.8 mg, 37.2 mg theoretical, 34.4%). LC-MS m/z 354.3 (M+1).

Example 91



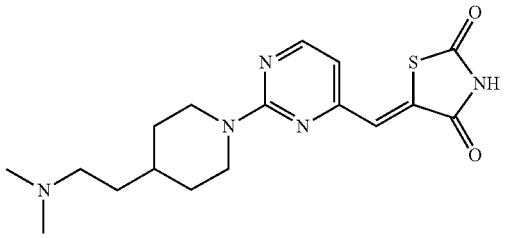
(Z)-5-((2-(3,4-dihydro-1H-pyrido[4,3-b]indol-2(5H)-yl) pyrimidin-4-yl)methylene)thiazolidine-2,4-dione was prepared using the general displacement procedure and 2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indole (4.2 mg, 39.7 mg theoretical, 10.6%). LC-MS m/z 378.4 (M+1).

Example 92



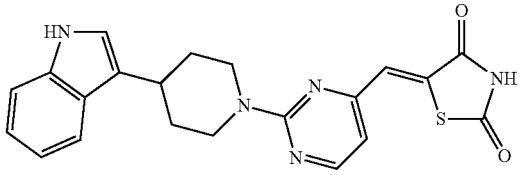
(Z)-5-((2-(((1-methylpiperidin-4-yl)methyl)amino)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione was prepared using the general displacement procedure and 1-(methylpiperidin-4-yl)methanamine (7.4 mg, 29.2 mg theoretical, 25.3%). LC-MS m/z 334.1 (M+1).

Example 93



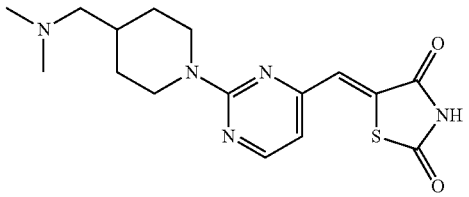
(Z)-5-((2-(4-(2-(dimethylamino)ethyl)piperidin-1-yl)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione was prepared using the general displacement procedure and N,N-dimethyl-2-(piperidin-4-yl)ethanamine (20.6 mg, 38.0 mg theoretical, 54.2%). LC-MS m/z 362.2 (M+1).

Example 94



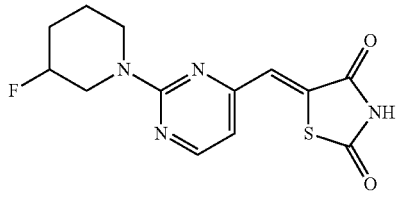
(Z)-5-((2-(4-(1H-indol-3-yl)piperidin-1-yl)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione was prepared using the general displacement procedure and 3-(piperidin-4-yl)-1H-indole (7.2 mg, 42.6 mg theoretical, 16.8%). LC-MS m/z 406.1 (M+1).

Example 95



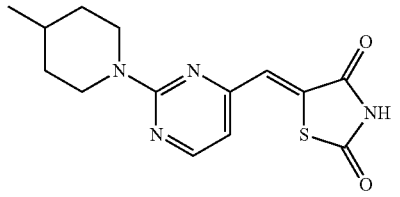
(Z)-5-((2-(4-(1H-indol-3-yl)piperidin-1-yl)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione was prepared using the general displacement procedure and N,N-dimethyl-1-(piperidin-4-yl)methanamine (23.1 mg, 36.5 mg theoretical, 63.2%). LC-MS m/z 348.1 (M+1).

Example 96



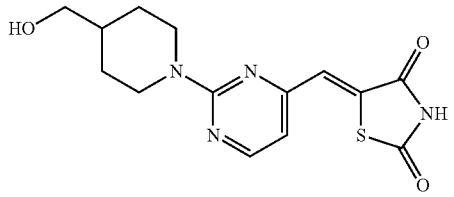
(Z)-5-((2-(3-fluoropiperidin-1-yl)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione was prepared using the general displacement procedure and 3-fluoropiperidine (7.7 mg, 32.4 mg theoretical, 23.7%). LC-MS m/z 309.1 (M+1).

Example 97



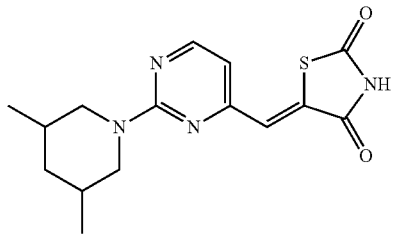
(Z)-5-((2-(4-methylpiperidin-1-yl)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione was prepared using the general displacement procedure and 4-methylpiperidine (16.4 mg, 32 mg theoretical, 51.2%). LC-MS m/z 305.1 (M+1).

Example 98



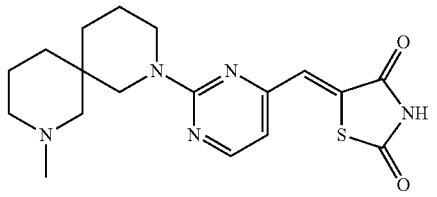
(Z)-5-((2-(4-(hydroxymethyl)piperidin-1-yl)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione was prepared using the general displacement procedure and piperidin-4-ylmethanol (17.8 mg, 33.7 mg theoretical, 52.8%). LC-MS m/z 321.1 (M+1).

Example 99



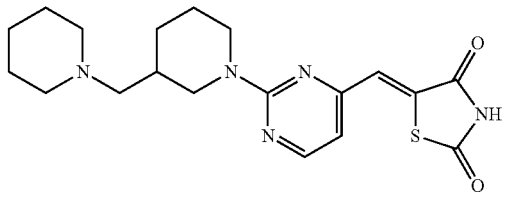
(Z)-5-((2-(3,5-dimethylpiperidin-1-yl)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione was prepared using the general displacement procedure and 3,5-dimethylpiperidine (1.3 mg, 33.5 mg theoretical, 3.9%). LC-MS m/z 319.1 (M+1).

Example 100



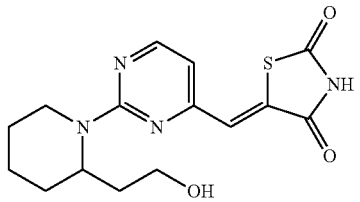
(Z)-5-((2-(8-methyl-2,8-diazaspiro[5.5]undecan-2-yl)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione was prepared using the general displacement procedure and 2-methyl-2,8-diazaspiro[5.5]undecane (23.5 mg, 39.3 mg theoretical, 59.8%). LC-MS m/z 374.2 (M+1).

Example 101



(Z)-5-((2-(3-(piperidin-1-ylmethyl)piperidin-1-yl)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione was prepared using the general displacement procedure and 1-(piperidin-3-ylmethyl)piperidine (21.8 mg, 40.7 mg theoretical, 53.5%). LC-MS m/z 388.5 (M+1).

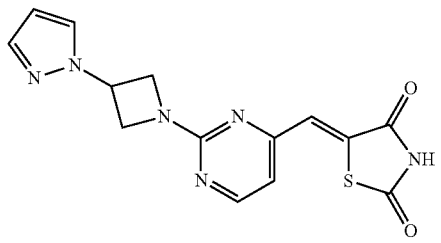
Example 102



(Z)-5-((2-(2-(2-hydroxyethyl)piperidin-1-yl)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione was prepared using the

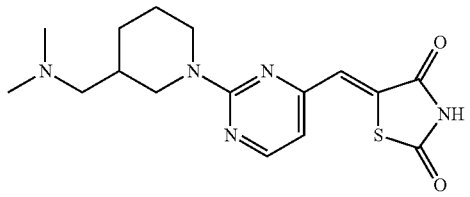
general displacement procedure and 2-(piperidin-2-yl)ethanol (10.1 mg, 35.2 mg theoretical, 28.7%). LC-MS m/z 335.1 (M+1).

Example 103



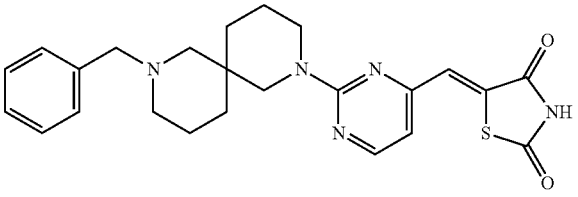
(Z)-5-((2-(3-(1H-pyrazol-1-yl)azetidin-1-yl)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione was prepared using the general displacement procedure and 1-(azetidin-3-yl)-1H-pyrazole (24.3 mg, 34.5 mg theoretical, 70.4%). LC-MS m/z 329.1 (M+1).

Example 104



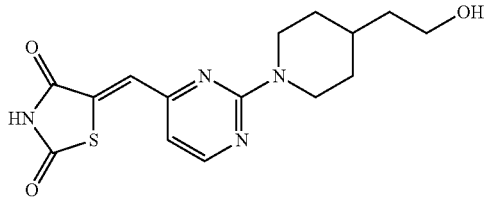
(Z)-5-((2-(3-((dimethylamino)methyl)piperidin-1-yl)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione was prepared using the general displacement procedure and N,N-dimethyl-1-(piperidin-3-yl)methanamine (23.4 mg, 36.5 mg theoretical, 64.1%). LC-MS m/z 348.4 (M+1).

Example 105



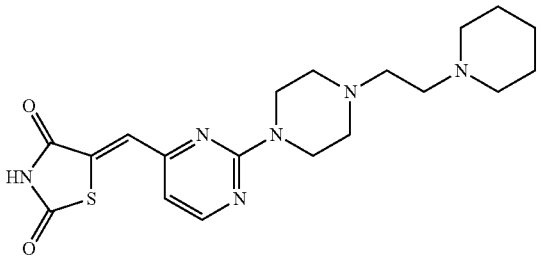
(Z)-5-((2-(8-benzyl-2,8-diazaspiro[5.5]undecan-2-yl)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione was prepared using the general displacement procedure and 2-benzyl-2,8-diazaspiro[5.5]undecane (15.3 mg, 47.3 mg theoretical, 32.4%). LC-MS m/z 450.5 (M+1).

Example 106



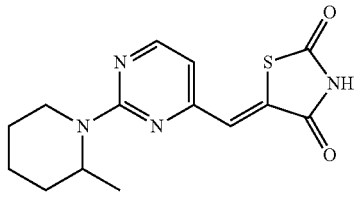
(Z)-5-((2-(4-(2-hydroxyethyl)piperidin-1-yl)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione was prepared using the general displacement procedure and 2-(piperidin-4-yl)ethanol (18.1 mg, 47.2 mg theoretical, 38.4%). LC-MS m/z 335.1 (M+1).

Example 107



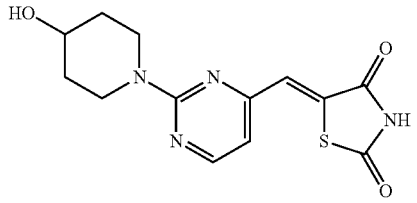
(Z)-5-((2-(4-(2-(piperidin-1-yl)ethyl)piperazin-1-yl)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione was prepared using the general displacement procedure and 1-(2-(piperidin-1-yl)ethyl)piperazine (36.6 mg, 66.3 mg theoretical, 55.2%). LC-MS m/z 403.2 (M+1).

Example 108



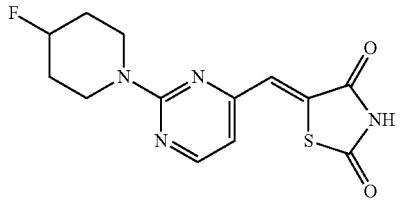
(Z)-5-((2-(2-methylpiperidin-1-yl)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione was prepared using the general displacement procedure and 2-methylpiperidine (2.5 mg, 32 mg theoretical, 7.8%). LC-MS m/z 305.1 (M+1).

Example 109



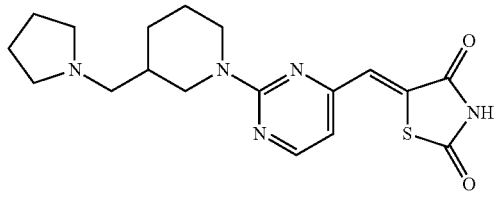
(Z)-5-((2-(4-hydroxypiperidin-1-yl)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione was prepared using the general displacement procedure and piperidin-4-ol (19.9 mg, 33.7 mg theoretical, 52.8%). LC-MS m/z 321.1 (M+1).

Example 110



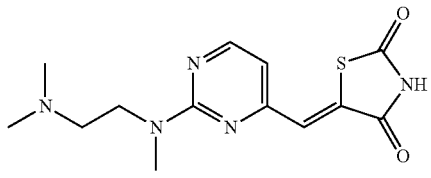
(Z)-5-((2-(4-fluoropiperidin-1-yl)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione was prepared using the general displacement procedure and 4-fluoropiperidine (12 mg, 32.4 mg theoretical, 37%). LC-MS m/z 309.1 (M+1).

Example 111



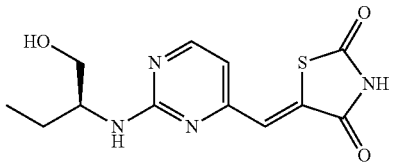
(Z)-5-((2-(3-(pyrrolidin-1-ylmethyl)piperidin-1-yl)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione was prepared using the general displacement procedure and 3-(pyrrolidin-1-ylmethyl)piperidine (4.3 mg, 39.3 mg theoretical, 11%). LC-MS m/z 374.5 (M+1).

Example 112



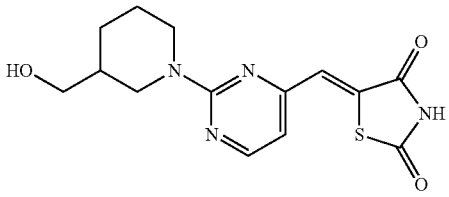
(Z)-5-((2-((2-(dimethylamino)ethyl)(methyl)amino)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione was prepared using the general displacement procedure and N1,N1,N2-trimethylethane-1,2-diamine (5.6 mg, 32.3 mg theoretical, 17.3%). LC-MS m/z 308.4 (M+1).

Example 113



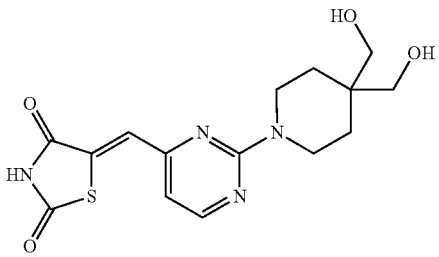
(S,Z)-5-((2-((1-hydroxybutan-2-yl)amino)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione was prepared using the general displacement procedure and amine (6.6 mg, 30.9 mg theoretical, 21.3%). LC-MS m/z 295.1 (M+1).

Example 114



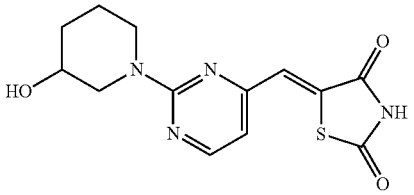
(Z)-5-((2-(3-(hydroxymethyl)piperidin-1-yl)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione was prepared using the general displacement procedure and (S)-2-aminobutan-1-ol (13.5 mg, 33.7 mg theoretical, 40.1%). LC-MS m/z 321.1 (M+1).

Example 115



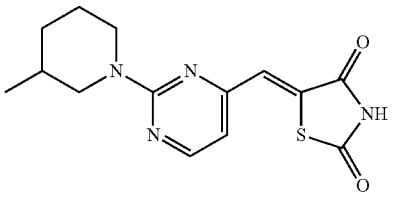
(Z)-5-((2-(4,4-bis(hydroxymethyl)piperidin-1-yl)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione was prepared using the general displacement procedure and piperidine-4,4-diyldimethanol (10 mg, 36.8 mg theoretical, 27.1%). LC-MS m/z 351.1 (M+1).

Example 116



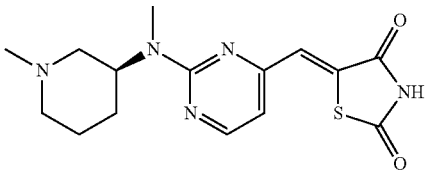
(Z)-5-((2-(3-hydroxypiperidin-1-yl)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione was prepared using the general displacement procedure and piperidin-3-ol (6.3 mg, 32.2 mg theoretical, 19.6%). LC-MS m/z 307.1 (M+1).

Example 117



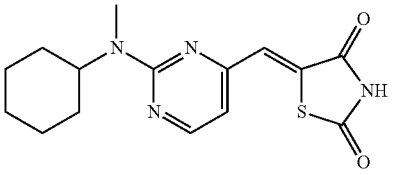
(Z)-5-((2-(3-methylpiperidin-1-yl)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione was prepared using the general displacement procedure and 3-methylpiperidine (10.3 mg, 32 mg theoretical, 32.2%). LC-MS m/z 305.1 (M+1).

Example 118



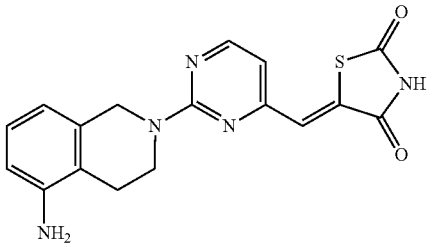
(S,Z)-5-((2-(methyl(1-methylpiperidin-3-yl)amino)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione was prepared using the general displacement procedure and (S)—N,1-dimethylpiperidin-3-amine (11.2 mg, 58.4 mg theoretical, 19.2%). LC-MS m/z 334.1 (M+1).

Example 119



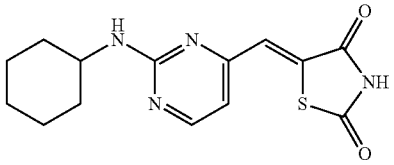
(Z)-5-((2-(cyclohexyl(methyl)amino)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione was prepared using the general displacement procedure and N-methylcyclohexanamine (3.4 mg, 33.5 mg theoretical, 10.2%). LC-MS m/z 319.1 (M+1).

Example 120



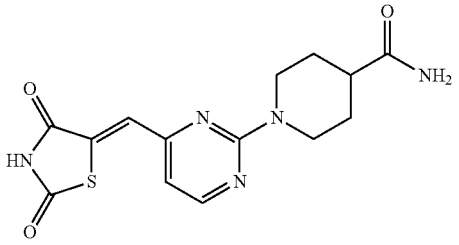
(Z)-5-((2-(5-amino-3,4-dihydroisoquinolin-2(1H)-yl)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione was prepared using the general displacement procedure and 1,2,3,4-tetrahydroisoquinolin-5-amine (8.2 mg, 37.2 mg theoretical, 22%). LC-MS m/z 354.1 (M+1).

Example 121



(Z)-5-((2-(cyclohexylamino)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione was prepared using the general displacement procedure and cyclohexanamine (3.6 mg, 32 mg theoretical, 11.2%). LC-MS m/z 305.1 (M+1).

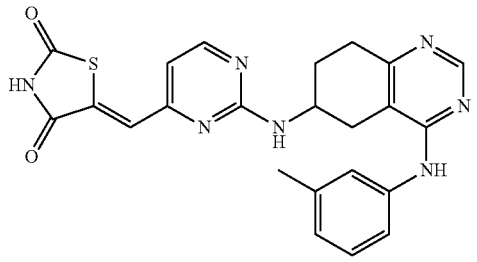
Example 122



(Z)-1-(4-((2,4-dioxothiazolidin-5-ylidene)methyl)pyrimidin-2-yl)piperidine-4-carboxamide was prepared using the

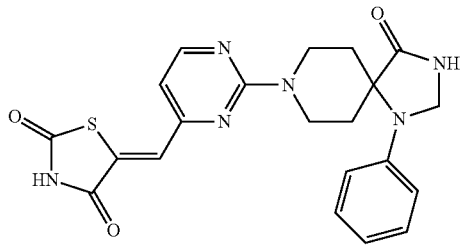
general displacement procedure and piperidine-4-carboxamide (16.7 mg, 35.1 mg theoretical, 47.6%). LC-MS m/z 334.1 (M+1).

Example 123



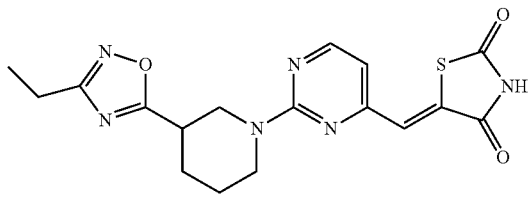
(Z)-5-((2-((4-(m-tolylamino)-5,6,7,8-tetrahydroquinazolin-6-yl)amino)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione was prepared using the general displacement procedure and N4-(m-tolyl)-5,6,7,8-tetrahydroquinazoline-4,6-diamine (5.2 mg, 48.3 mg theoretical, 10.8%). LC-MS m/z 460.5 (M+1).

Example 124



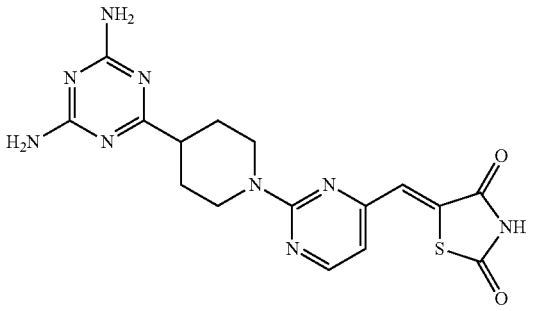
(Z)-5-((2-(4-oxo-1-phenyl-1,3,8-triazaspiro[4.5]decan-8-yl)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione was prepared using the general displacement procedure and 1-phenyl-1,3,8-triazaspiro[4.5]decan-4-one (12.4 mg, 38.2 mg theoretical, 32.4%). LC-MS m/z 437.1 (M+1).

Example 125



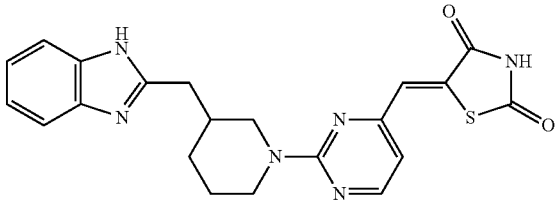
(Z)-5-((2-(3-(3-ethyl-1,2,4-oxadiazol-5-yl)piperidin-1-yl)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione was prepared using the general displacement procedure and 3-ethyl-5-(piperidin-3-yl)-1,2,4-oxadiazole (11.9 mg, 33.9 mg theoretical, 35.1%). LC-MS m/z 387.1 (M+1).

Example 126



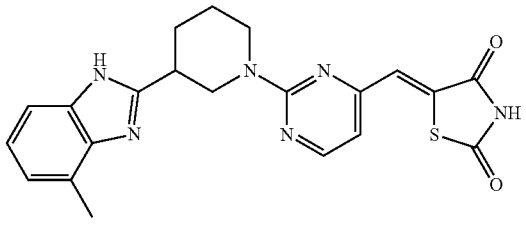
(Z)-5-((2-(4-(4,6-diamino-1,3,5-triazin-2-yl)piperidin-1-yl)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione was prepared using the general displacement procedure and 6-(piperidin-4-yl)-1,3,5-triazine-2,4-diamine (13.0 mg, 35.0 mg theoretical, 37.1%). LC-MS m/z 400.1 (M+1).

Example 127



(Z)-5-((2-(3-((1H-benzo[d]imidazol-2-yl)methyl)piperidin-1-yl)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione was prepared using the general displacement procedure and 2-(piperidin-3-ylmethyl)-1H-benzo[d]imidazole (29.3 mg, 44.2 mg theoretical, 66.3%). LC-MS m/z 421.5 (M+1).

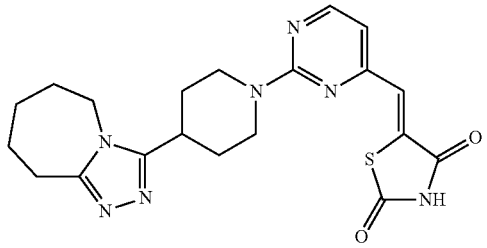
Example 128



(Z)-5-((2-(3-(4-methyl-1H-benzo[d]imidazol-2-yl)piperidin-1-yl)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione was prepared using the general displacement procedure and

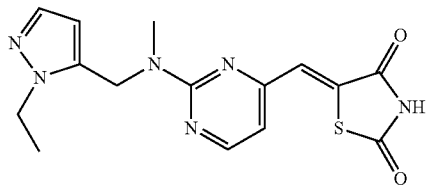
4-methyl-2-(piperidin-3-yl)-1H-benzo[d]imidazole (18.9 mg, 44.2 mg theoretical, 42.7%). LC-MS m/z 421.5 (M+1).

Example 129



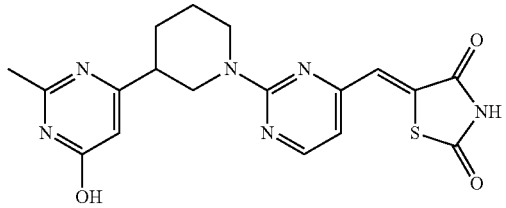
(Z)-5-((2-(4-(6,7,8,9-tetrahydro-5H-[1,2,4]triazolo[4,3-a]azepin-3-yl)piperidin-1-yl)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione was prepared using the general displacement procedure and 3-(piperidin-4-yl)-6,7,8,9-tetrahydro-5H-[1,2,4]triazolo[4,3-a]azepine (16.2 mg, 44.7 mg theoretical, 36.2%). LC-MS m/z 426.5 (M+1).

Example 130



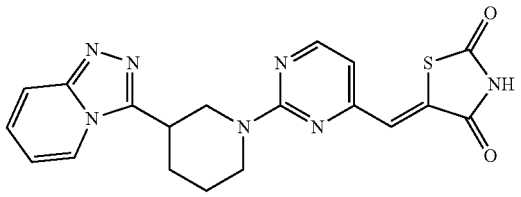
(Z)-5-((2-(((1-ethyl-1H-pyrazol-5-yl)methyl)(methyl)amino)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione was prepared using the general displacement procedure and 1-(1-ethyl-1H-pyrazol-5-yl)-N-methylmethanamine (7.2 mg, 36.2 mg theoretical, 20%). LC-MS m/z 345.1 (M+1).

Example 131



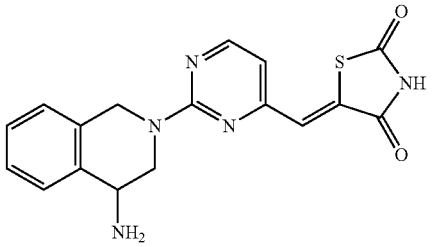
(Z)-5-((2-(3-(6-hydroxy-2-methylpyrimidin-4-yl)piperidin-1-yl)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione was prepared using the general displacement procedure and 2-methyl-6-(piperidin-3-yl)pyrimidin-4-ol (16.8 mg, 41.9 mg theoretical, 40.1%). LC-MS m/z 399.1 (M+1).

Example 132



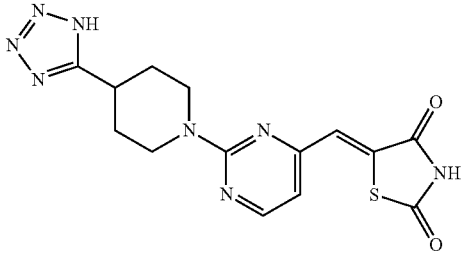
(Z)-5-((2-(3-([1,2,4]triazolo[4,3-a]pyridin-3-yl)piperidin-1-yl)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione was prepared using the general displacement procedure and 3-(piperidin-3-yl)-[1,2,4]triazolo[4,3-a]pyridine (11 mg, 42.8 mg theoretical, 25.7%). LC-MS m/z 408.5 (M+1).

Example 133



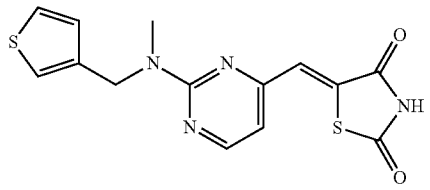
(Z)-5-((2-(4-amino-3,4-dihydroisoquinolin-2(1H)-yl)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione was prepared using the general displacement procedure and 1,2,3,4-tetrahydroisoquinolin-4-amine (1.4 mg, 37.2 mg theoretical, 3.8%). LC-MS m/z 354.1 (M+1).

Example 134



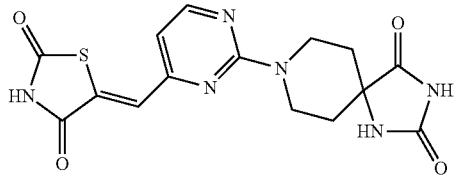
(Z)-5-((2-(4-(1H-tetrazol-5-yl)piperidin-1-yl)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione was prepared using the general displacement procedure and 4-(1H-tetrazol-5-yl)piperidine (4 mg, 37.7 mg theoretical, 10.6%). LC-MS m/z 359.1 (M+1).

Example 135



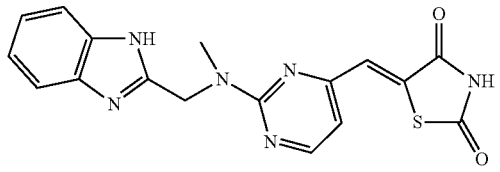
(Z)-5-((2-(methyl(thiophen-3-ylmethyl)amino)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione was prepared using the general displacement procedure and N-methyl-1-(thiophen-3-yl)methanamine (7.5 mg, 35 mg theoretical, 21.5%). LC-MS m/z 333.0 (M+1).

Example 136



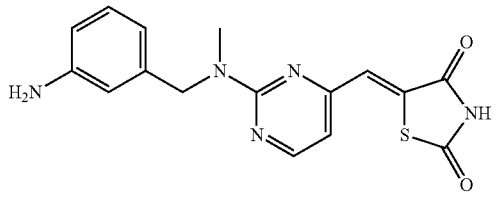
(Z)-5-((2-(2,4-dioxo-1,3,8-triazaspiro[4.5]decan-8-yl)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione was prepared using the general displacement procedure and 1,3,8-triazaspiro[4.5]decane-2,4-dione (15.2 mg, 39.4 mg theoretical, 38.6%). LC-MS m/z 375.1 (M+1).

Example 137



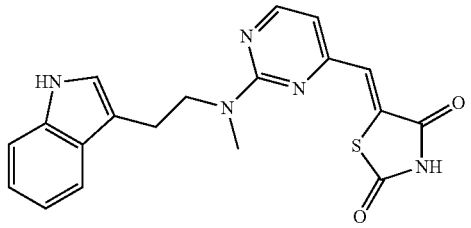
(Z)-5-((2-(((1H-benzo[d]imidazol-2-yl)methyl)(methyl)amino)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione was prepared using the general displacement procedure and 1-(1H-benzo[d]imidazol-2-yl)-N-methylmethanamine (6.6 mg, 38.5 mg theoretical, 17%). LC-MS m/z 367.1 (M+1).

Example 138



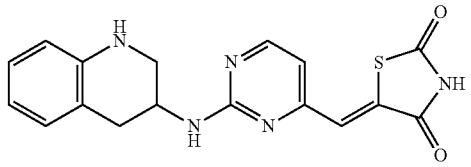
(Z)-5-((2-((3-aminobenzyl)(methyl)amino)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione was prepared using the general displacement procedure and 3-((methylamino)methyl)aniline (19.7 mg, 35.9 mg theoretical, 54.9%). LC-MS m/z 342.1 (M+1).

Example 139



(Z)-5-((2-((2-(1H-indol-3-yl)ethyl)(methyl)amino)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione was prepared using the general displacement procedure and 2-(1H-indol-3-yl)-N-methylethanamine (8.3 mg, 39.9 mg theoretical, 20.8%). LC-MS m/z 380.4 (M+1).

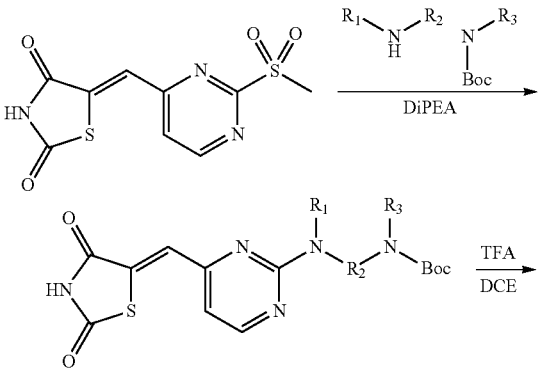
Example 140



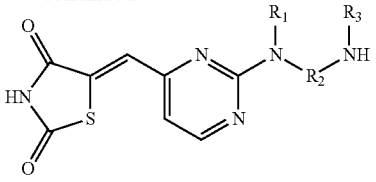
(Z)-5-((2-((1,2,3,4-tetrahydroquinolin-3-yl)amino)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione was prepared using the general displacement procedure and 1,2,3,4-tetrahydroquinolin-3-amine (5 mg, 37.2 mg theoretical, 13.5%). LC-MS m/z 354.1 (M+1).

Example 141

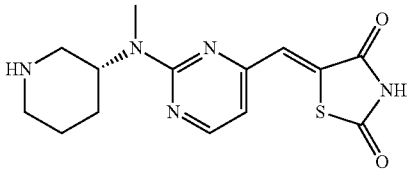
Displacement/De-protection of Mono-Boc Diamines



-continued

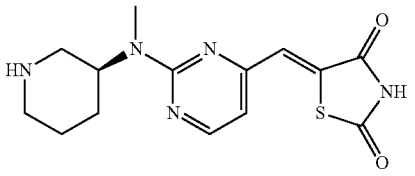


Example 142



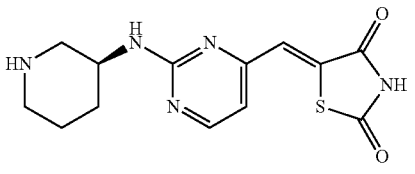
(R,Z)-5-((2-(methyl(piperidin-3-yl)amino)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione was prepared using the general displacement procedure and (R)-tert-butyl 3-(methylamino)piperidine-1-carboxylate. The crude protected amine was then treated with 2 mL DCE and 500 μL of TFA and shaken for 24 h. The solvent was removed under reduced pressure (Genevac HT-4) and the crude residues were purified using reverse phase HPLC (MS-triggered fraction collection) with an acetonitrile/water or methanol/water gradient and trifluoroacetic acid as a modifier. The pure fractions were then concentrated under reduced pressure (Genevac HT-4) (3.1 mg, 55.9 mg theoretical, 5.5%). LC-MS m/z 320.1 (M+1).

Example 143



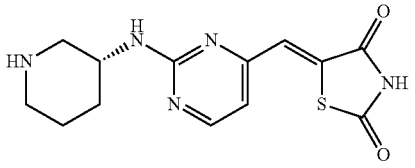
(S,Z)-5-((2-(methyl(piperidin-3-yl)amino)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione was prepared using the general displacement procedure and (S)-tert-butyl 3-(methylamino)piperidine-1-carboxylate. The crude protected amine was then treated with 2 mL DCE and 500 μL of TFA and shaken for 24 h. The solvent was removed under reduced pressure (Genevac HT-4) and the crude residues were purified using reverse phase HPLC (MS-triggered fraction collection) with an acetonitrile/water or methanol/water gradient and trifluoroacetic acid as a modifier. The pure fractions were then concentrated under reduced pressure (Genevac HT-4) (3.2 mg, 55.9 mg theoretical, 5.7%). LC-MS m/z 320.1 (M+1).

Example 144



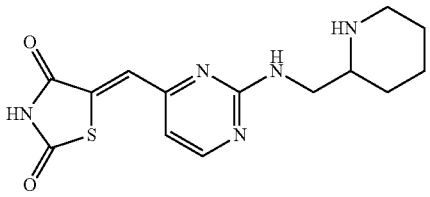
(S,Z)-5-((2-(piperidin-3-ylamino)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione was prepared using the general displacement procedure and (R)-tert-butyl 3-aminopiperidine-1-carboxylate. The crude protected amine was then treated with 2 mL DCE and 500 μL of TFA and shaken for 24 h. The solvent was removed under reduced pressure (Genevac HT-4) and the crude residues were purified using reverse phase HPLC (MS-triggered fraction collection) with an acetonitrile/water or methanol/water gradient and trifluoroacetic acid as a modifier. The pure fractions were then concentrated under reduced pressure (Genevac HT-4) (6.9 mg, 32.1 mg theoretical, 21.5%). LC-MS m/z 306.1 (M+1).

Example 145



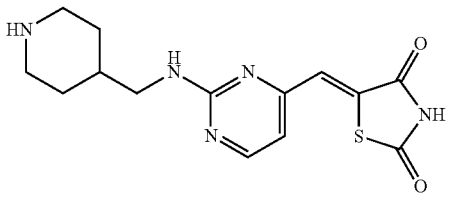
(R,Z)-5-((2-(piperidin-3-ylamino)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione was prepared using the general displacement procedure and (S)-tert-butyl 3-aminopiperidine-1-carboxylate. The crude protected amine was then treated with 2 mL DCE and 500 μL of TFA and shaken for 24 h. The solvent was removed under reduced pressure (Genevac HT-4) and the crude residues were purified using reverse phase HPLC (MS-triggered fraction collection) with an acetonitrile/water or methanol/water gradient and trifluoroacetic acid as a modifier. The pure fractions were then concentrated under reduced pressure (Genevac HT-4) (3.8 mg, 32.1 mg theoretical, 11.8%). LC-MS m/z 306.1 (M+1).

Example 146



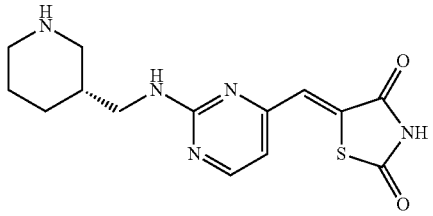
(Z)-5-((2-((piperidin-2-ylmethyl)amino)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione was prepared using the general displacement procedure and tert-butyl 2-(aminomethyl)piperidine-1-carboxylate. The crude protected amine was then treated with 2 mL DCE and 500 μL of TFA and shaken for 24 h. The solvent was removed under reduced pressure (Genevac HT-4) and the crude residues were purified using reverse phase HPLC (MS-triggered fraction collection) with an acetonitrile/water or methanol/water gradient and trifluoroacetic acid as a modifier. The pure fractions were then concentrated under reduced pressure (Genevac HT-4) (10.7 mg, 45.6 mg theoretical, 23.5%). LC-MS m/z 320.1 (M+1).

Example 147



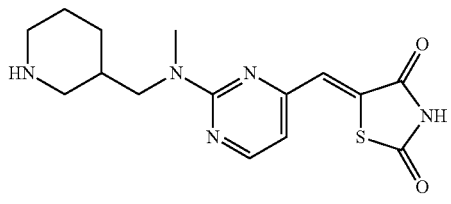
(Z)-5-((2-((piperidin-4-ylmethyl)amino)pyrimidin-4-yl) methylene)thiazolidine-2,4-dione was prepared using the general displacement procedure and tert-butyl 4-(aminomethyl)piperidine-1-carboxylate. The crude protected amine was then treated with 2 mL DCE and 500 μL of TFA and shaken for 24 h. The solvent was removed under reduced pressure (Genevac HT-4) and the crude residues were purified using reverse phase HPLC (MS-triggered fraction collection) with an acetonitrile/water or methanol/water gradient and trifluoroacetic acid as a modifier. The pure fractions were then concentrated under reduced pressure (Genevac HT-4) (5.3 mg, 33.5 mg theoretical, 15.8%). LC-MS m/z 320.1 (M+1).

Example 148



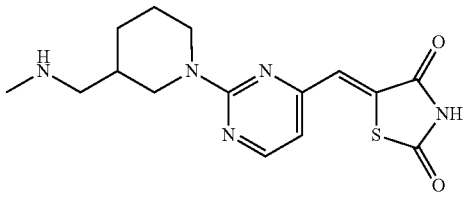
(R,Z)-5-((2-((piperidin-3-ylmethyl)amino)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione was prepared using the general displacement procedure and (S)-tert-butyl 3-(aminomethyl)piperidine-1-carboxylate. The crude protected amine was then treated with 2 mL DCE and 500 μL of TFA and shaken for 24 h. The solvent was removed under reduced pressure (Genevac HT-4) and the crude residues were purified using reverse phase HPLC (MS-triggered fraction collection) with an acetonitrile/water or methanol/water gradient and trifluoroacetic acid as a modifier. The pure fractions were then concentrated under reduced pressure (Genevac HT-4) (7.3 mg, 33.5 mg theoretical, 21.8%). LC-MS m/z 320.1 (M+1).

Example 149



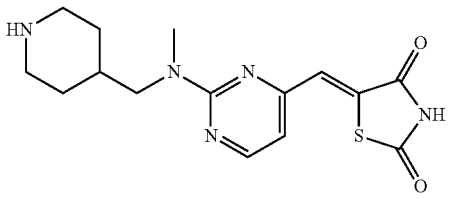
(Z)-5-((2-(methyl(piperidin-3-ylmethyl)amino)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione was prepared using the general displacement procedure and tert-butyl 3-((methylamino)methyl)piperidine-1-carboxylate. The crude protected amine was then treated with 2 mL DCE and 500 μL of TFA and shaken for 24 h. The solvent was removed under reduced pressure (Genevac HT-4) and the crude residues were purified using reverse phase HPLC (MS-triggered fraction collection) with an acetonitrile/water or methanol/water gradient and trifluoroacetic acid as a modifier. The pure fractions were then concentrated under reduced pressure (Genevac HT-4) (21.6 mg, 35 mg theoretical, 61.7%). LC-MS m/z 334.1 (M+1).

Example 150



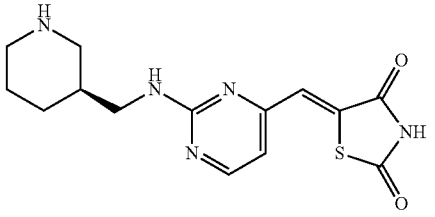
(Z)-5-((2-(3-((methylamino)methyl)piperidin-1-yl)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione was prepared using the general displacement procedure and tert-butyl methyl(piperidin-3-ylmethyl)carbamate. The crude protected amine was then treated with 2 mL DCE and 500 μL of TFA and shaken for 24 h. The solvent was removed under reduced pressure (Genevac HT-4) and the crude residues were purified using reverse phase HPLC (MS-triggered fraction collection) with an acetonitrile/water or methanol/water gradient and trifluoroacetic acid as a modifier. The pure fractions were then concentrated under reduced pressure (Genevac HT-4) (17.9 mg, 35 mg theoretical, 51.1%). LC-MS m/z 334.1 (M+1).

Example 151



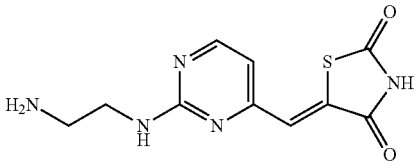
(Z)-5-((2-(methyl(piperidin-4-ylmethyl)amino)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione was prepared using the general displacement procedure and tert-butyl 4-((methylamino)methyl)piperidine-1-carboxylate. The crude protected amine was then treated with 2 mL DCE and 500 μL of TFA and shaken for 24 h. The solvent was removed under reduced pressure (Genevac HT-4) and the crude residues were purified using reverse phase HPLC (MS-triggered fraction collection) with an acetonitrile/water or methanol/water gradient and trifluoroacetic acid as a modifier. The pure fractions were then concentrated under reduced pressure (Genevac HT-4) (6.5 mg, 35 mg theoretical, 18.6%). LC-MS m/z 334.1 (M+1).

Example 152



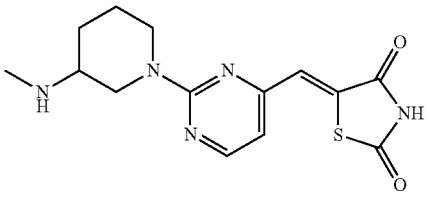
(S,Z)-5-((2-((piperidin-3-ylmethyl)amino)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione was prepared using the general displacement procedure and (R)-tert-butyl 3-((methylamino)methyl)piperidine-1-carboxylate. The crude protected amine was then treated with 2 mL DCE and 500 μL of TFA and shaken for 24 h. The solvent was removed under reduced pressure (Genevac HT-4) and the crude residues were purified using reverse phase HPLC (MS-triggered fraction collection) with an acetonitrile/water or methanol/water gradient and trifluoroacetic acid as a modifier. The pure fractions were then concentrated under reduced pressure (Genevac HT-4) (11.2 mg, 33.5 mg theoretical, 33.4%). LC-MS m/z 320.1 (M+1).

Example 153



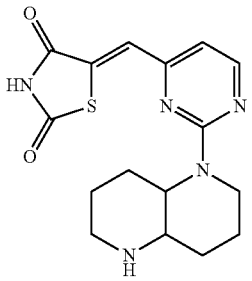
(Z)-5-((2-((2-aminoethyl)amino)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione was prepared using the general displacement procedure and tert-butyl (2-aminoethyl)carbamate. The crude protected amine was then treated with 2 mL DCE and 500 μL of TFA and shaken for 24 h. The solvent was removed under reduced pressure (Genevac HT-4) and the crude residues were purified using reverse phase HPLC (MS-triggered fraction collection) with an acetonitrile/water or methanol/water gradient and trifluoroacetic acid as a modifier. The pure fractions were then concentrated under reduced pressure (Genevac HT-4) (10.7 mg, 27.9 mg theoretical, 38.4%). LC-MS m/z 266.1 (M+1).

Example 154



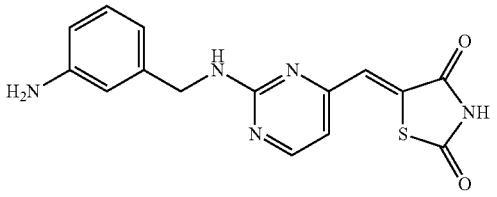
(Z)-5-((2-(3-(methylamino)piperidin-1-yl)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione was prepared using the general displacement procedure and tert-butyl methyl(piperidin-3-yl)carbamate. The crude protected amine was then treated with 2 mL DCE and 500 μL of TFA and shaken for 24 h. The solvent was removed under reduced pressure (Genevac HT-4) and the crude residues were purified using reverse phase HPLC (MS-triggered fraction collection) with an acetonitrile/water or methanol/water gradient and trifluoroacetic acid as a modifier. The pure fractions were then concentrated under reduced pressure (Genevac HT-4) (26.9 mg, 33.5 mg theoretical, 80%). LC-MS m/z 320.1 (M+1).

Example 155



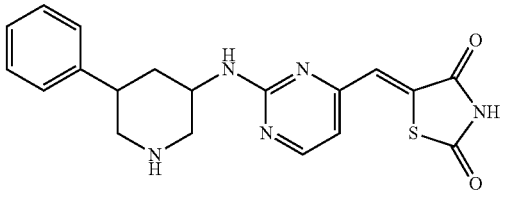
(Z)-5-((2-(octahydro-1,5-naphthyridin-1(2H)-yl)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione was prepared using the general displacement procedure and tert-butyl octahydro-1,5-naphthyridine-1(2H)-carboxylate. The crude protected amine was then treated with 2 mL DCE and 500 μL of TFA and shaken for 24 h. The solvent was removed under reduced pressure (Genevac HT-4) and the crude residues were purified using reverse phase HPLC (MS-triggered fraction collection) with an acetonitrile/water or methanol/water gradient and trifluoroacetic acid as a modifier. The pure fractions were then concentrated under reduced pressure (Genevac HT-4) (7.2 mg, 36.3 mg theoretical, 19.8%). LC-MS m/z 346.1 (M+1).

Example 156



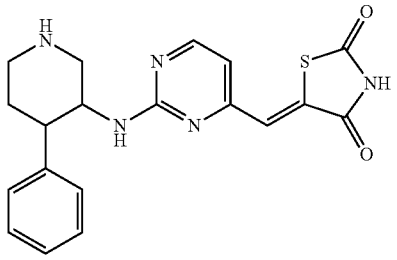
(Z)-5-((2-((3-aminobenzyl)amino)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione was prepared using the general displacement procedure and tert-butyl (3-(aminomethyl)phenyl)carbamate. The crude protected amine was then treated with 2 mL DCE and 500 μL of TFA and shaken for 24 h. The solvent was removed under reduced pressure (Genevac HT-4) and the crude residues were purified using reverse phase HPLC (MS-triggered fraction collection) with an acetonitrile/water or methanol/water gradient and trifluoroacetic acid as a modifier. The pure fractions were then concentrated under reduced pressure (Genevac HT-4) (6.5 mg, 28.7 mg theoretical, 22.7%). LC-MS m/z 328.1 (M+1).

Example 157



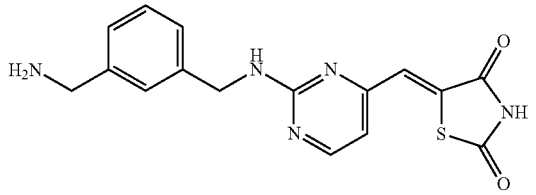
(Z)-5-((2-((5-phenylpiperidin-3-yl)amino)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione was prepared using the general displacement procedure and tert-butyl 3-amino-5-phenylpiperidine-1-carboxylate. The crude protected amine was then treated with 2 mL DCE and 500 μL of TFA and shaken for 24 h. The solvent was removed under reduced pressure (Genevac HT-4) and the crude residues were purified using reverse phase HPLC (MS-triggered fraction collection) with an acetonitrile/water or methanol/water gradient and trifluoroacetic acid as a modifier. The pure fractions were then concentrated under reduced pressure (Genevac HT-4) (5.6 mg, 33.4 mg theoretical, 16.8%). LC-MS m/z 382.1 (M+1).

Example 158



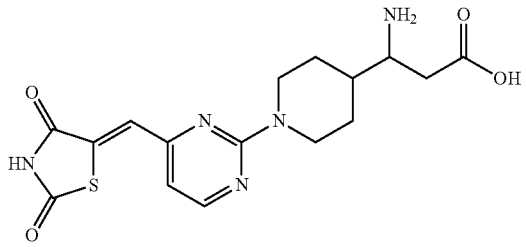
(Z)-5-((2-((4-phenylpiperidin-3-yl)amino)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione was prepared using the general displacement procedure and tert-butyl 3-amino-4-phenylpiperidine-1-carboxylate. The crude protected amine was then treated with 2 mL DCE and 500 μL of TFA and shaken for 24 h. The solvent was removed under reduced pressure (Genevac HT-4) and the crude residues were purified using reverse phase HPLC (MS-triggered fraction collection) with an acetonitrile/water or methanol/water gradient and trifluoroacetic acid as a modifier. The pure fractions were then concentrated under reduced pressure (Genevac HT-4) (5.7 mg, 33.4 mg theoretical, 17.1%). LC-MS m/z 382.1 (M+1).

Example 159



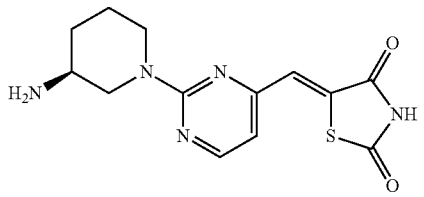
(Z)-5-((2-((3-(aminomethyl)benzyl)amino)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione was prepared using the general displacement procedure and tert-butyl 3-(aminomethyl)benzylcarbamate. The crude protected amine was then treated with 2 mL DCE and 500 μL of TFA and shaken for 24 h. The solvent was removed under reduced pressure (Genevac HT-4) and the crude residues were purified using reverse phase HPLC (MS-triggered fraction collection) with an acetonitrile/water or methanol/water gradient and trifluoroacetic acid as a modifier. The pure fractions were then concentrated under reduced pressure (Genevac HT-4) (16.6 mg, 35.8 mg theoretical, 46.3%). LC-MS m/z 342.1 (M+1).

Example 160



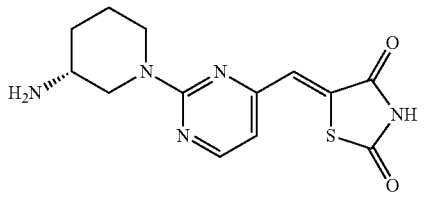
(Z)-5-((2-(octahydro-1,5-naphthyridin-1(2H)-yl)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione was prepared using the general displacement procedure and 3-((tert-butoxycarbonyl)amino)-3-(piperidin-4-yl)propanoic acid. The crude protected amine was then treated with 2 mL DCE and 500 μL of TFA and shaken for 24 h. The solvent was removed under reduced pressure (Genevac HT-4) and the crude residues were purified using reverse phase HPLC (MS-triggered fraction collection) with an acetonitrile/water or methanol/water gradient and trifluoroacetic acid as a modifier. The pure fractions were then concentrated under reduced pressure (Genevac HT-4) (24.6 mg, 11.8 mg theoretical, 208%). LC-MS m/z 378.4 (M+1).

Example 161



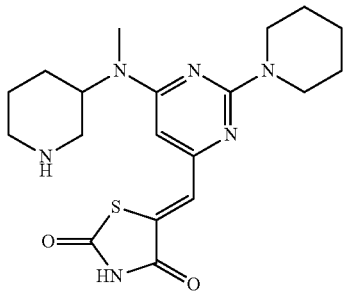
(S,Z)-5-((2-(3-aminopiperidin-1-yl)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione was prepared using the general displacement procedure and (S)-tert-butyl piperidin-3-ylcarbamate. The crude protected amine was then treated with 2 mL DCE and 500 μL of TFA and shaken for 24 h. The solvent was removed under reduced pressure (Genevac HT-4) and the crude residues were purified using reverse phase HPLC (MS-triggered fraction collection) with an acetonitrile/water or methanol/water gradient and trifluoroacetic acid as a modifier. The pure fractions were then concentrated under reduced pressure (Genevac HT-4) (46.8 mg, 30.2 mg theoretical, 155%). LC-MS m/z 306.1 (M+1).

Example 162



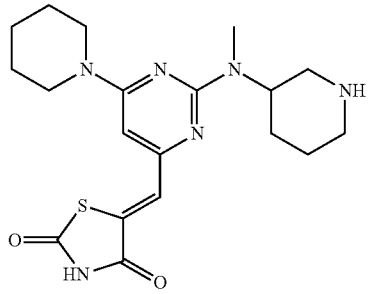
(R,Z)-5-((2-(3-aminopiperidin-1-yl)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione was prepared using the general displacement procedure and (R)-tert-butyl piperidin-3-ylcarbamate. The crude protected amine was then treated with 2 mL DCE and 500 μL of TFA and shaken for 24 h. The solvent was removed under reduced pressure (Genevac HT-4) and the crude residues were purified using reverse phase HPLC (MS-triggered fraction collection) with an acetonitrile/water or methanol/water gradient and trifluoroacetic acid as a modifier. The pure fractions were then concentrated under reduced pressure (Genevac HT-4) (44.2 mg, 30.2 mg theoretical, 146%). LC-MS m/z 306.1 (M+1).

Example 163



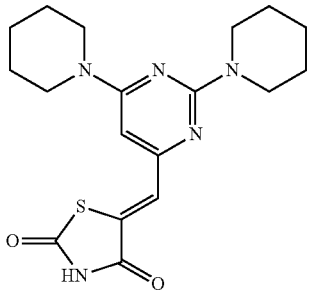
(Z)-5-β6-(methyl(piperidin-3-yl)amino)-2-(piperidin-1-yl)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione was prepared using General Procedure 2 for the Preparation of Amino-Analogs (Example 81) using tert-butyl 3-(methylamino)piperidine-1-carboxylate and piperidine (11.4 mg, 54.0 mg theoretical, 21.1%). LC-MS m/z 403.2 (M+1).

Example 164



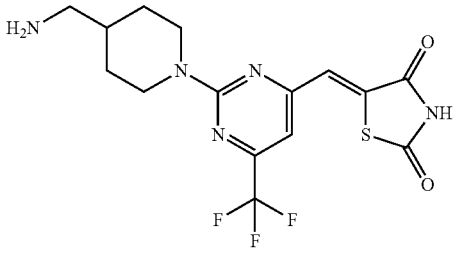
(Z)-5-((2-(methyl(piperidin-3-yl)amino)-6-(piperidin-1-yl)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione was prepared using General Procedure 2 for the Preparation of Amino-Analogs (Example 81) using piperidine and tert-Butyl 3-(methylamino)piperidine-1-carboxylate (10.5 mg, 26.3 mg theoretical, 41.9%). LC-MS m/z 403.2 (M+1).

Example 165

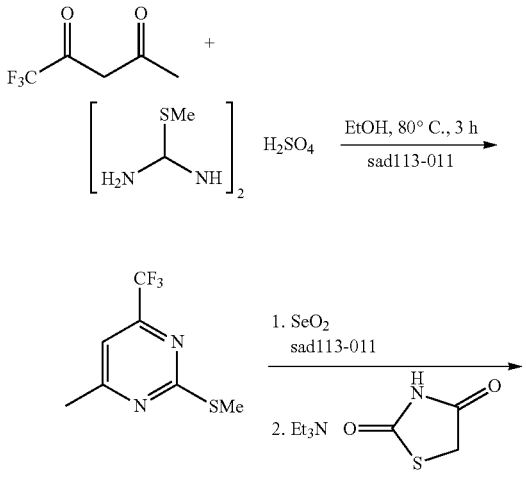


(Z)-5-((2,6-di(piperidin-1-yl)pyrimidin-4-yl)methylene) thiazolidine-2,4-dione was prepared using General Procedure 2 for the Preparation of Amino-Analogs (Example 81) using piperidine (14.0 mg, 233 mg theoretical, 6%). LC-MS m/z 374.2 (M+1).

Example 166



(Z)-5-((2-(4-(aminomethyl)piperidin-1-yl)-6-(trifluoromethyl)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione was prepared as follows.



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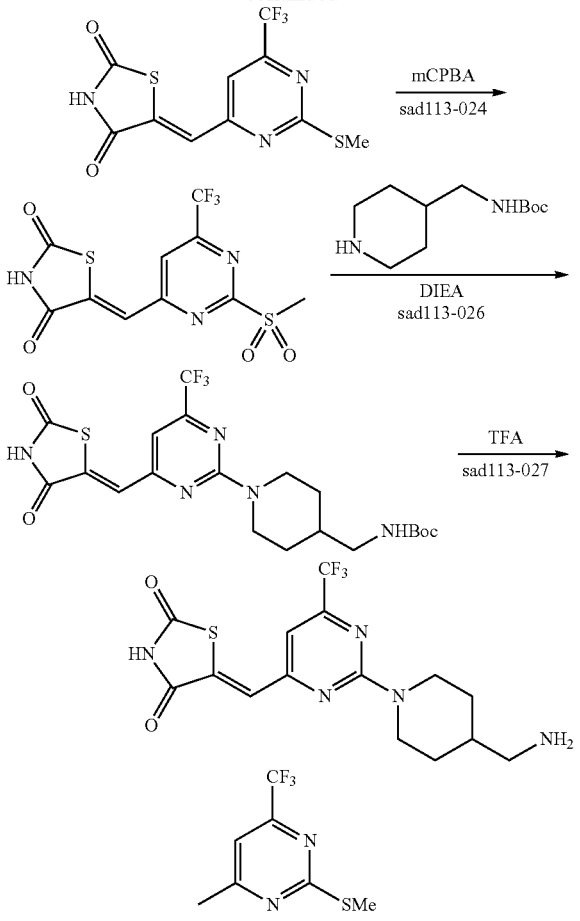
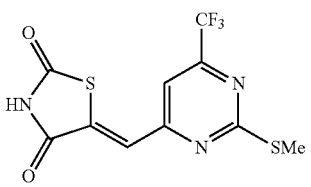


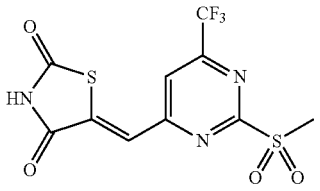
4-Methyl-2-(methylthio)-6-(trifluoromethyl)pyrimidine

A 30 mL round-bottomed vial was charged with 1,1,1-trifluoropentane-2,4-dione (2.00 g, 13.0 mmol, 1 equiv.), ethanol (15 mL, 0.8 M), thiomethylisourea hemi sulfuric acid salt (1.807 g, 6.5 mmol, 1 equiv.) and the reaction mixture was shaken at 80° C. for 3 h. The solvent was concentrated under reduced pressure and the residue was partitioned between CH_2Cl_2 (25 mL) and saturated $NaHCO_3$ (25 mL). The aqueous layer was extracted with EtOAc (2×10 mL) and the combined organic layer was dried over Na_2SO_4 and concentrated under reduced pressure to provide the crude desired pyrimidine as a slightly orange solid. Purification using the Biotage (SiO_2, 25 g cartridge, Hexanes/EtOAc 95:5 to 75:25) afforded 1.66 g of the pure desired product (2.70 g theoretical, 61.4%). LC-MS m/z 209 (M+1).



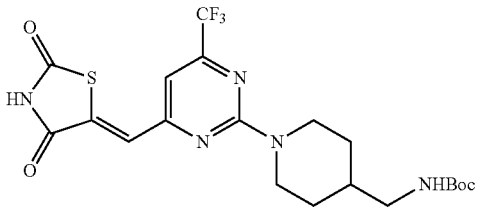
(Z)-5-((2-(Methylthio)-6-(trifluoromethyl)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione

A 30 mL round-bottomed vial was charged with 4-methyl-2-(methylthio)-6-(trifluoromethyl)pyrimidine (0.500 g, 2.4 mmol, 1 equiv.), ethanol (5 mL, 0.48 M), selenium dioxide (0.293 mg, 2.6 mmol, 1.1 equiv.), and the reaction mixture was shaken at 90° C. for 40 h and then RT for 14 d. The crude reaction mixture was then treated with thiazolidine-2,4-dione (0.281 g, 2.4 mmol, 1 equiv.), triethylamine (1.0 mL, 7.20 mmol, 3 equiv.) and the reaction mixture was shaken for 16 h at 80° C. The solvent was concentrated under reduced pressure and the residue was partitioned between EtOAc (30 mL) and saturated $NaHCO_3$ (25 mL). The aqueous layer was extracted with EtOAc (2×10 mL) and the combined organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified using the Biotage (SiO_2, 10 g cartridge, CH_2Cl_2/MeOH 99:1 to 9:1) that afforded 270 mg of partially purified product that was re-purified using the Biotage (SiO_2, 10 g cartridge, Hexanes/EtOAc 90:10 to 0:1 then CH_2Cl_2/MeOH 99:1 to 9:1) afforded 212 mg of yellow solid that was still not completely pure but was used directly in the next step without further purification.



(Z)-5-((2-(Methylsulfonyl)-6-(trifluoromethyl)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione

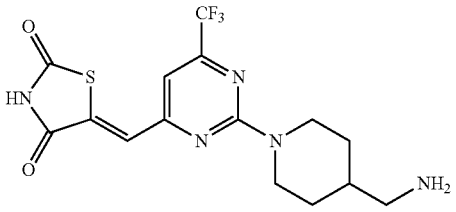
An 8 mL round-bottomed vial was charged with the pyrimidine sulfide (212 mg, 0.66 mmol, 1 equiv.), CH_2Cl_2 (3 mL, 0.22 M), m-CPBA 50% by weight (0.683 g, 1.98 mmol, 3 equiv.) was added over a 1 min. period at RT. After 3.5 h, an additional 3 equivalents of m-CPBA 50% by weight (0.683 g, 1.98 mmol, 3 equiv.) was added and the reaction mixture was stirred at RT overnight. The resulting white solid was filtered and washed with CH_2Cl_2 and then with Et_2O to provide 67 mg of an off-white solid (233 mg theoretical, 28.7%), which was used in the next step without further purification. LC-MS m/z 354 (M+1).



(Z)-tert-Butyl ((1-(4-((2,4-dioxothiazolidin-5-ylidene)methyl)-6-(trifluoromethyl)pyrimidin-2-yl)piperidin-4-yl)methyl)carbamate

An 8 mL round-bottomed vial was charged with the 2-sulfone pyrimidine (67 mg, 0.19 mmol, 1 equiv.), DMSO (1 mL,

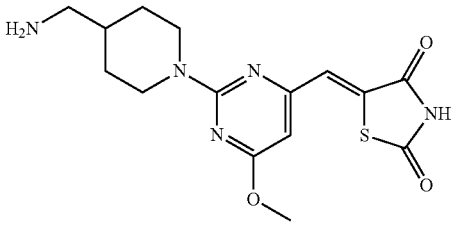
0.19M), tert-Butyl (piperidin-4-ylmethyl)carbamate (40.6 mg, 0.19 mmol, 1 equiv.), DIPEA (66 μL, 0.38 mmol, 2 equiv.), and the reaction mixture was stirred for 1 h at RT and then 50° C. for 3 h. The reaction was directly purified using reverse phase HPLC (2 injections of 500 μL, 12 min method, methanol/water gradient with 0.4% TFA) to afford the desired product (15.3 mg, 92.7 mg theoretical, 16.5%).



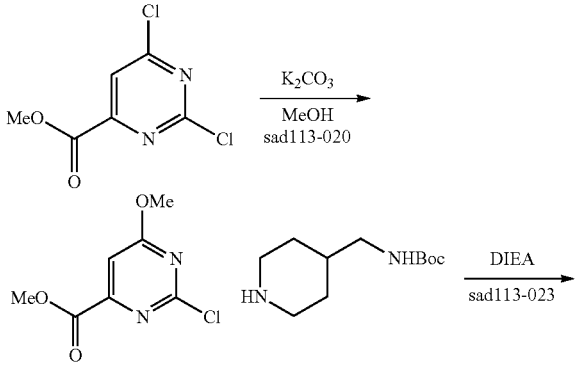
(Z)-5-((2-(4-(aminomethyl)piperidin-1-yl)-6-(trifluoromethyl)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione

An 8 mL round-bottomed vial was charged with the CF_3-pyrimidine (15.3 mg, 0.031 mmol, 1 equiv.), CH_2Cl_2 (1 mL, 0.03 M), TFA (0.5 mL, 6.5 mmol, 208 equiv.), and the reaction mixture was stirred for 1 h at RT. The solvent was concentrated under reduced pressure and the residue was dried under high vacuum. The residue was washed with ether (2×2 mL) and the yellow solid was dried under high vacuum overnight to afford (13.4 mg, 15.8 mg theoretical, 85%). LC-MS m/z 388.1 (M+1).

Example 167



(Z)-5-((2-(4-(aminomethyl)piperidin-1-yl)-6-methoxypyrimidin-4-yl)methylene)thiazolidine-2,4-dione was prepared as follows.



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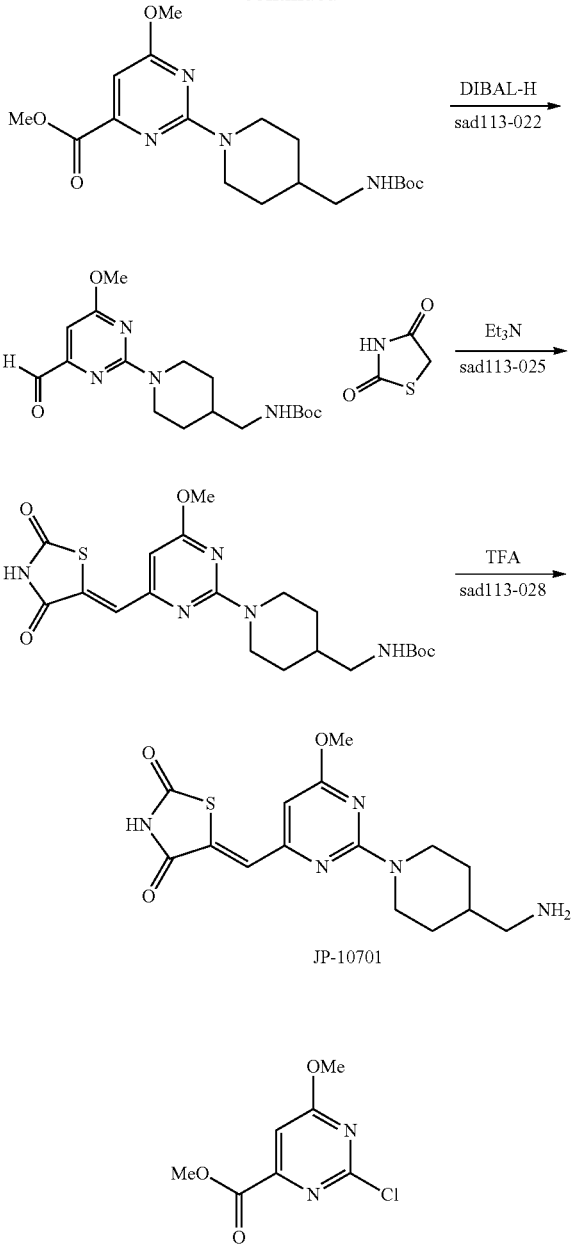
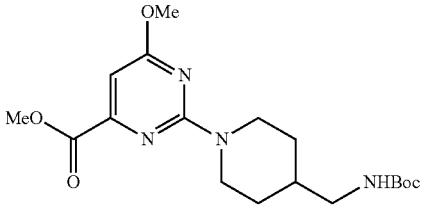


JP-10701

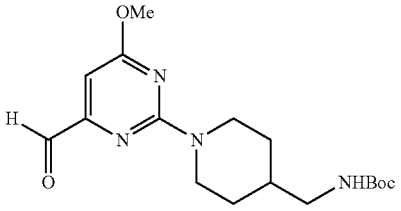
Methyl 2-chloro-6-methoxypyrimidine-4-carboxylate

A 30 mL round-bottomed vial was charged with methyl 2,6-dichloropyrimidine-4-carboxylate (0.6 g, 2.9 mmol, 1 equiv.), methanol (6 mL, 0.97 M), K_2CO_3 (0.401 g, 2.9 mmol, 1 equiv.), and the reaction mixture was shaken at 65° C. for 1.5 h. The solvent was concentrated under reduced pressure and the residue was partitioned between EtOAc (25 mL) and H_2O (25 mL) and the water layer was extracted with EtOAc (2×20 mL). The combined organic layer was dried over Na_2SO_4 and concentrated under reduced pressure to provide the crude chloropyrimidine (441 mg, 588 mg theoretical, 75%), which was used in the next step without further purification.



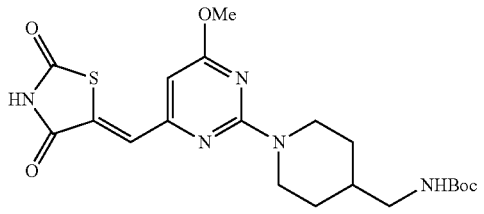
Methyl 2-(4-(((tert-butoxycarbonyl)amino)methyl) piperidin-1-yl)-6-methoxypyrimidine-4-carboxylate

An 8 mL round-bottomed vial was charged with the 2-chloropyrimidine (150 mg, 0.74 mmol, 1.5 equiv.), methanol (1.5 mL, 0.49 M), tert-Butyl (piperidin-4-ylmethyl)carbamate (159 mg, 0.49 mmol, 1 equiv.), DIPEA (258 μL, 0.99 mmol, 2 equiv.), and the reaction mixture was shaken at 65° C. for 3 h. The solvent was concentrated under reduced pressure and the residue was partitioned between EtOAc (25 mL) and saturated $NaHCO_3$ (10 mL). The organic layer was dried over Na_2SO_4 and dried under reduced pressure to provide the crude product. Purification using the Biotage (SiO_2, 10 g cartridge, Hexanes/EtOAc 95:5 to 40:60) afforded the desired pyrimidine intermediate as a white solid (219 mg, 281 mg theoretical, 78%).



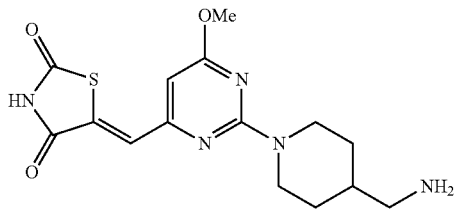
tert-Butyl ((1-(4-formyl-6-methoxypyrimidin-2-yl) piperidin-4-yl)methyl)carbamate

A 50 mL 2-neck round-bottomed flask was charged with the methyl ester intermediate (150 mg, 0.39 mmol, 1 equiv.), CH_2Cl_2 (2 mL, 0.195 M), and then DIBAL-H 1 M in CH_2Cl_2 (0.59 mL, 0.59 mmol, 1.5 equiv.) was added over a 4 minute period at −78° C. The reaction was then stirred for 1.5 h at −78° C. and for 1.5 h between −78° C. and RT. LC-MS showed mostly starting material so the reaction mixture was re-cooled to −78° C. and DIBAL-H (0.8 mL, 0.8 mmol, 2 equiv.) was added. LC-MS showed mostly starting material. The reaction mixture was stored at −20° C. for 3 d. The reaction mixture was cooled to −78° C. and treated with 1M DIBAL-H in hexanes (0.59 mL, 0.59 mmol, 1 equiv.) over a 5 min. period, which produced a white precipitate. After 2.5 h, another equivalent of DiBAL-H (1 M in Hexanes, 0.59 mL) was added over a 15 min. period at −78° C. The reaction was quenched at −78° C. after 35 min. with methanol (1 mL). The solvent were concentrated under reduced pressure and the residue was partitioned between CH_2Cl_2 (20 mL) and saturated $NaHCO_3$ (20 mL). The organic layer was dried over Na_2SO_4 and the solvent was concentrated under reduced pressure to provide the crude product, which was used in the next step without further purification.



(Z)-tert-Butyl ((1-(4-((2,4-dioxothiazolidin-5-ylidene)methyl)-6-methoxypyrimidin-2-yl)piperidin-4-yl)methyl)carbamate

An 8 mL round-bottomed vial was charged with the crude aldehyde (0.2 mmol, estimated), ethanol (2 mL), thiazolidine-2,4-dione (23 mg, 0.2 mmol, 1 equiv.), triethylamine (56 μL, 0.4 mmol, 2 equiv.), purged with Ar, and the reaction mixture was shaken at 80° C. for 24 h. The crude mixture was purified using the Biotage (SiO_2, 10 g cartridge, CH_2Cl_2/MeOH 99:1 to 94:6) afforded 113 mg of the partially purified product. The sample was re-purified using reverse phase HPLC (methanol/water 10-90%, 0.4% TFA, 3 equal injections) provided the pure product as a TFA salt (47.3 mg, 225 mg theoretical, 21%). LC-MS m/z 450 (M+1).

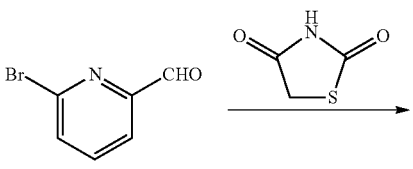


(Z)-5-((2-(4-(aminomethyl)piperidin-1-yl)-6-methoxypyrimidin-4-yl)methylene)thiazolidine-2,4-dione

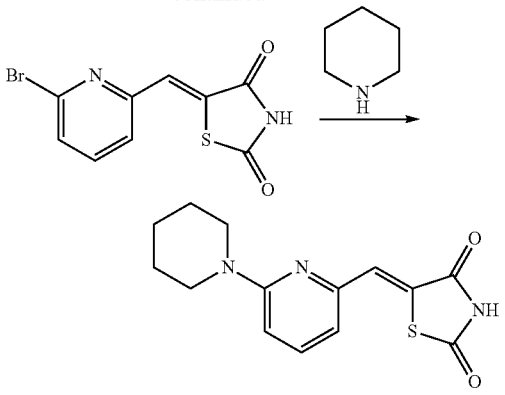
An 8 mL round-bottomed vial was charged with the MeO-pyrimidine boc protected amine (47.3 mg, 105 μmol, 1 equiv.), CH_2Cl_2 (1.3 mL, 0.08 M), TFA (0.5 mL, 6.5 mmol, 62 equiv.), and the reaction mixture was stirred for 1 h at RT. The solvents were concentrated under reduced pressure and the residue was re-dissolved in DMSO (0.9 mL) and purified by reverse phase HPLC (methanol/water with 0.4% TFA, 10-90% method, 2 injections of 500 μL) to provide as the TFA salt (43.9 mg, 48.8 mg theoretical, 90%). LC-MS m/z 350.1 (M+1).

Example 168

Synthesized Pyridine Analogs



-continued



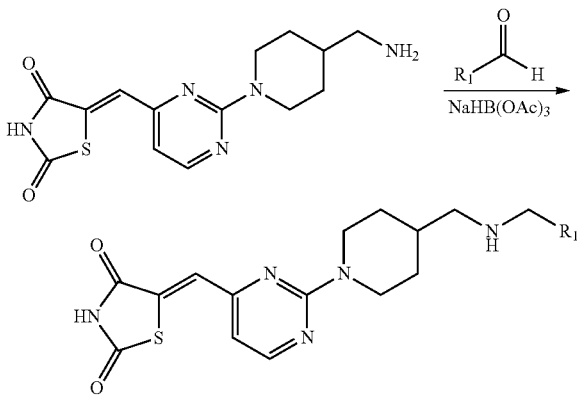
(Z)-5-((6-(piperidin-1-yl)pyridin-2-yl)methylene)thiazolidine-2,4-dione was prepared as follows.

A 30 mL round-bottomed vial was charged with thiazolidine-2,4-dione (300 mg, 2.56 mmol, 1 equiv.), toluene (5 mL, 0.5 M), 6-bromopicolinaldehyde (477 mg, 2.56 mmol, 1 equiv.), glacial acetic acid (22 μL, 0.256 mmol, 0.1 equiv.), piperidine (25 μL, 0.256 mmol, 0.1 equiv.), purged with Ar, and heated with shaking at 125° C. After heating for 16 h, the yellow reaction solution was pipeted away from the solid precipitate. The precipitate was washed with acetone (3×5 mL) and dried under high vacuum to afford the desired product as a solid (439 mg, 731 mg theoretical, 60%), which was used in the next step without further purification.

A 2 dram round-bottomed vial was charged with (Z)-5-((6-bromopyridin-2-yl)methylene)thiazolidine-2,4-dione (60 mg, 0.210 mmol, 1 equiv.), DMSO (1 mL, 0.08 M), diisopropylethylamine (34 μL, 0.2 mmol, 1 equiv.), and piperidine (21 μL, 0.21 mmol, 1 equiv.), and the reaction was heated with shaking at 110° C. for 24 h. The solvent was removed under reduced pressure (Genvac HT-4) and the crude residue was purified using reverse phase HPLC (MS-triggered fraction collection) with an acetonitrile/water gradient and trifluoroacetic acid as a modifier. The pure fractions were then concentrated under reduced pressure (Genevac HT-4) to provide (Z)-5-((6-(piperidin-1-yl)pyridin-2-yl)methylene)thiazolidine-2,4-dione (7.9 mg, 60.9 mg theoretical, 12.9%). LC-MS m/z 290.1 (M+1).

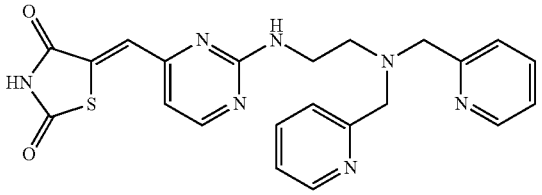
Example 169

Synthesized Reductive Amination Analogs



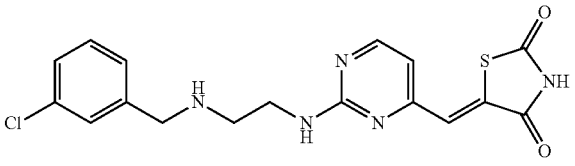
General Reductive Amination Procedure: A 2-dram round-bottomed vial was charged with the crude amine/TFA salt prepared using the general displacement procedure followed by the general TFA de-protection procedure (0.115 mmol), DCE (2 mL), DIPEA (6 eq. 0.690 mmol), DMF (1 mL), the aldehyde (1 equiv., 0.115 mmol), and the reaction mixture was shaken for 1 h at RT. The reaction mixture was then treated with $NaBH(OAc)_3$ (2.5 equiv., 0.230 mmol) and the reaction was shaken 16 h at RT. The reaction mixture was then diluted with DCE (2 mL) and $NaHCO_3$ (2 mL). The aqueous layer was back extracted with DCE (2×2 mL) and the combined organic layer was concentrated under reduced pressure (Genevac HT-4) and the crude residue was purified using reverse phase HPLC (MS-triggered fraction collection) with an acetonitrile/water or methanol/water gradient and trifluoroacetic acid as the modifier. The pure fractions were then concentrated under reduced pressure (Genevac HT-4) to afford the pure products as the TFA salt.

Example 170



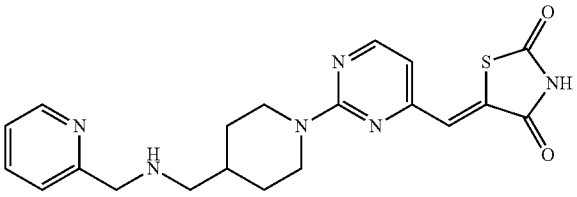
(Z)-5-((2-((2-(dimethylamino)ethyl)(methyl)amino)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione was prepared using the General Reductive Amination Procedure (Example 169) and picolinaldehyde (16.1 mg, 47 mg theoretical, 34.3%). LC-MS m/z 448.5 (M+1).

Example 171



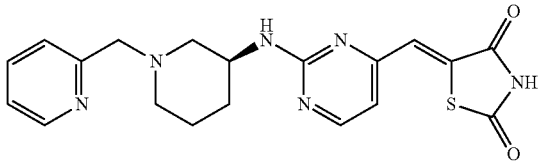
(Z)-5-((2-((2-((3-chlorobenzyl)amino)ethyl)amino)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione was prepared using the general General Reductive Amination Procedure (Example 169) and 3-chlorobenzaldehyde (5.6 mg, 40.9 mg theoretical, 13.7%). LC-MS m/z 390.8 (M+1).

Example 172



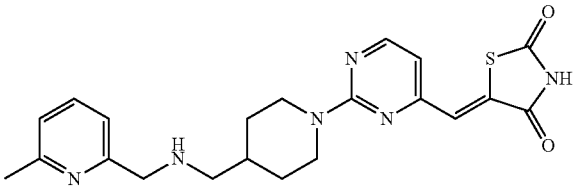
(Z)-5-((2-(4-(((pyridin-2-ylmethyl)amino)methyl)piperidin-1-yl)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione was prepared using the General Reductive Amination Procedure (Example 169) and picolinaldehyde (8.5 mg, 71.8 mg theoretical, 11.8%). LC-MS m/z 411.5 (M+1).

Example 173



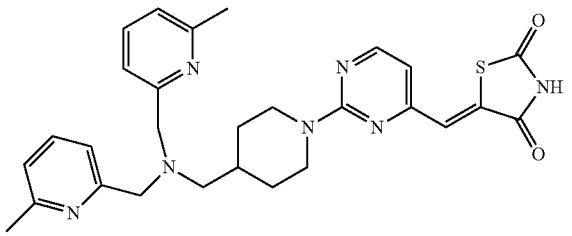
(S,Z)-5-((2-((1-(pyridin-2-ylmethyl)piperidin-3-yl)amino)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione was prepared using the General Reductive Amination Procedure (Example 169) and picolinaldehyde (2.6 mg, 34.7 mg theoretical, 7.1%). LC-MS m/z 397.1 (M+1).

Example 174



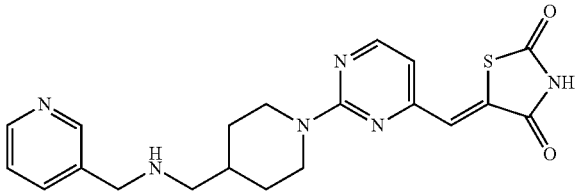
(Z)-5-((2-(4-((((6-methylpyridin-2-yl)methyl)amino)methyl)piperidin-1-yl)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione was prepared using the General Reductive Amination Procedure (Example 169) and 6-methylpicolinaldehyde (10.4 mg, 74.3 mg theoretical, 14%). LC-MS m/z 425.5 (M+1).

Example 175



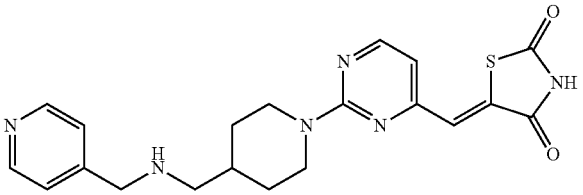
(Z)-5-((2-(4-((bis((6-methylpyridin-2-yl)methyl)amino)methyl)piperidin-1-yl)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione was prepared using the General Reductive Amination Procedure (Example 169) and 6-methylpicolinaldehyde (2.5 mg, 92.6 mg theoretical, 2.7%). LC-MS m/z 530.6 (M+1).

Example 176



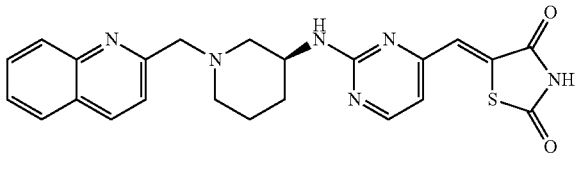
(Z)-5-((2-(4-(((pyridin-3-ylmethyl)amino)methyl)piperidin-1-yl)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione was prepared using the General Reductive Amination Procedure (Example 169) and nicotinaldehyde (5.3 mg, 71.8 mg theoretical, 7.4%). LC-MS m/z 411.5 (M+1).

Example 177



(Z)-5-((2-(4-(((pyridin-4-ylmethyl)amino)methyl)piperidin-1-yl)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione was prepared using the General Reductive Amination Procedure (Example 169) and isonicotinaldehyde (4.1 mg, 71.8 mg theoretical, 5.7%). LC-MS m/z 411.5 (M+1).

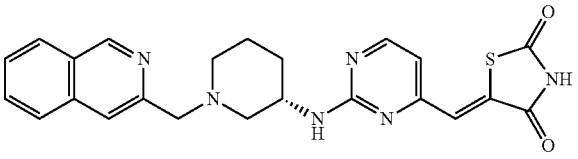
Example 178



(S,Z)-5-((2-((1-(quinolin-2-ylmethyl)piperidin-3-yl)amino)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione was prepared using the General Reductive Amination Proce-

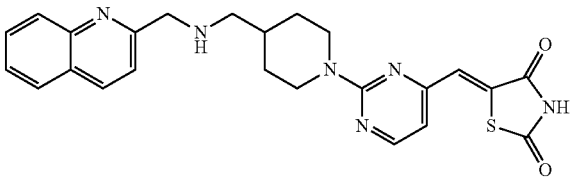
dure (Example 169) and quinoline-2-carbaldehyde (2.2 mg, 78 mg theoretical, 2.8%). LC-MS m/z 447.5 (M+1).

Example 179



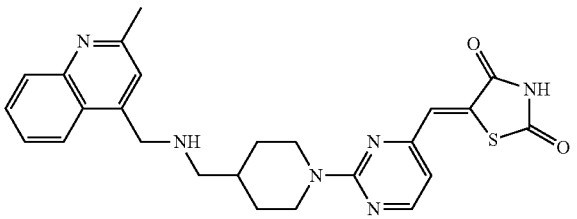
(S,Z)-5-((2-((1-(isoquinolin-3-ylmethyl)piperidin-3-yl)amino)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione was prepared using the General Reductive Amination Procedure (Example 169) and isoquinoline-3-carbaldehyde (1.5 mg, 78 mg theoretical, 1.9%). LC-MS m/z 447.5 (M+1).

Example 180



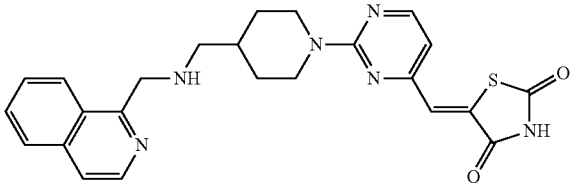
(Z)-5-((2-(4-(((quinolin-2-ylmethyl)amino)methyl)piperidin-1-yl)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione was prepared using the General Reductive Amination Procedure (Example 169) and quinoline-2-carbaldehyde (3.8 mg, 81 mg theoretical, 4.7%). LC-MS m/z 461.5 (M+1).

Example 181



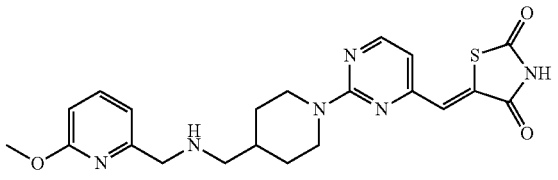
(Z)-5-((2-(4-((((2-methylquinolin-4-yl)methyl)amino)methyl)piperidin-1-yl)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione was prepared using the General Reductive Amination Procedure (Example 169) and 2-methylquinoline-4-carbaldehyde (35.1 mg, 56.5 mg theoretical, 62.2%). LC-MS m/z 475.5 (M+1).

Example 182



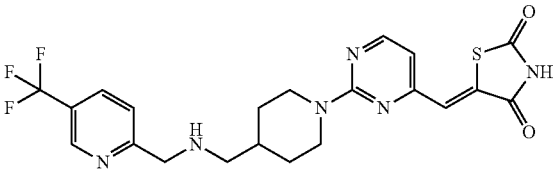
(Z)-5-((2-(4-(((isoquinolin-1-ylmethyl)amino)methyl)piperidin-1-yl)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione was prepared using the General Reductive Amination Procedure (Example 169) and isoquinoline-1-carbaldehyde (35.1 mg, 43.8 mg theoretical, 80%). LC-MS m/z 461.5 (M+1).

Example 183



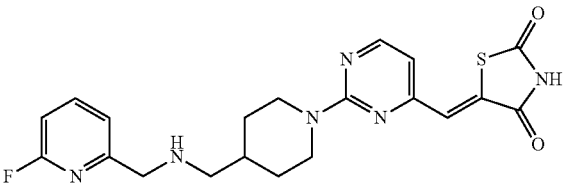
(Z)-5-((2-(4-((((6-methoxypyridin-2-yl)methyl)amino)methyl)piperidin-1-yl)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione was prepared using the General Reductive Amination Procedure (Example 169) and 6-methoxypicolinaldehyde (37.5 mg, 52.4 mg theoretical, 71.5%). LC-MS m/z 441.5 (M+1).

Example 184



(Z)-5-((2-(4-((((5-(trifluoromethyl)pyridin-2-yl)methyl)amino)methyl)piperidin-1-yl)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione was prepared using the General Reductive Amination Procedure (Example 169) and 5-(trifluoromethyl)picolinaldehyde (23 mg, 56.9 mg theoretical, 40.4%). LC-MS m/z 479.5 (M+1).

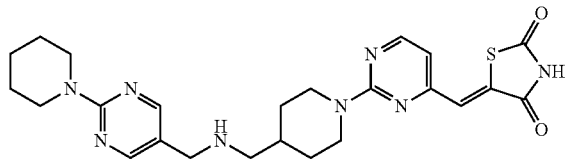
Example 185



(Z)-5-((2-(4-((((6-fluoropyridin-2-yl)methyl)amino)methyl)piperidin-1-yl)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione was prepared using the General Reductive Amina-

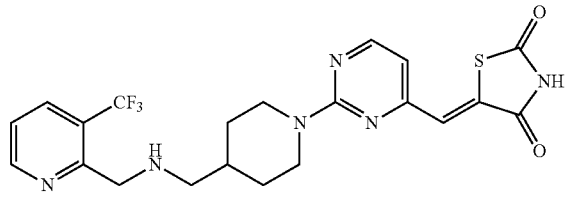
tion Procedure (Example 169) and 6-fluoropicolinaldehyde (29.3 mg, 51 mg theoretical, 57.5%). LC-MS m/z 429.5 (M+1).

Example 186



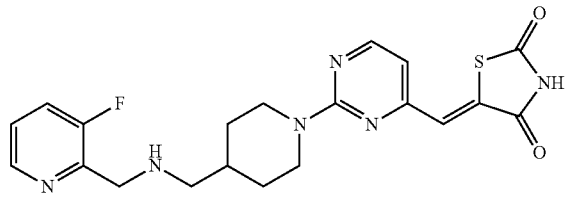
(Z)-5-((2-(4-((((2-(piperidin-1-yl)pyrimidin-5-yl)methyl)amino)methyl)piperidin-1-yl)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione was prepared using the General Reductive Amination Procedure (Example 169) and 2-(piperidin-1-yl)pyrimidine-5-carbaldehyde (40.1 mg, 47 mg theoretical, 80%). LC-MS m/z 495.5 (M+1).

Example 187



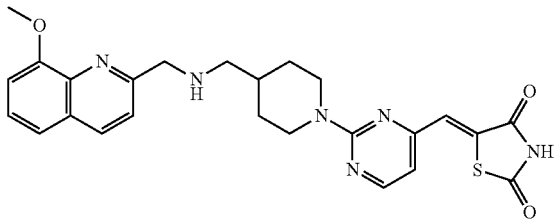
(Z)-5-((2-(4-((((3-(trifluoromethyl)pyridin-2-yl)methyl)amino)methyl)piperidin-1-yl)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione was prepared using the General Reductive Amination Procedure (Example 169) and 3-(trifluoromethyl)picolinaldehyde (44 mg, 45.5 mg theoretical, 97%). LC-MS m/z 479.5 (M+1).

Example 188



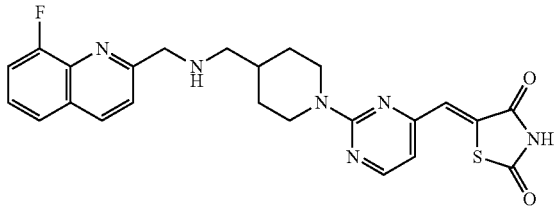
(Z)-5-((2-(4-((((3-fluoropyridin-2-yl)methyl)amino)methyl)piperidin-1-yl)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione was prepared using the General Reductive Amination Procedure (Example 169) and 3-fluoropicolinaldehyde (42.5 mg, 40.7 mg theoretical, 104%). LC-MS m/z 429.5 (M+1).

Example 189



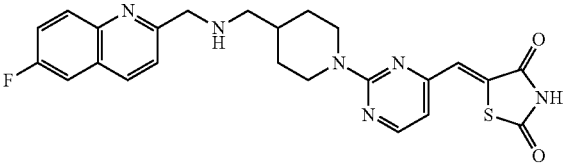
(Z)-5-((2-(4-((((8-methoxyquinolin-2-yl)methyl)amino)methyl)piperidin-1-yl)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione was prepared using the General Reductive Amination Procedure (Example 169) and 8-methoxyquinoline-2-carbaldehyde (35.5 mg, 46.6 mg theoretical, 76%). LC-MS m/z 491.5 (M+1).

Example 190



(Z)-5-((2-(4-((((8-fluoroquinolin-2-yl)methyl)amino)methyl)piperidin-1-yl)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione was prepared using the General Reductive Amination Procedure (Example 169) and 8-fluoroquinoline-2-carbaldehyde (28.5 mg, 45.5 mg theoretical, 62.7%). LC-MS m/z 479.5 (M+1).

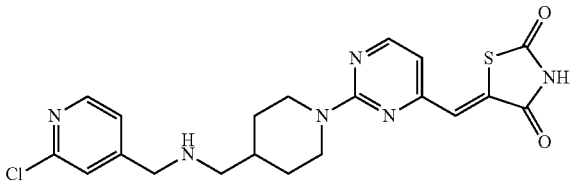
Example 191



(Z)-5-((2-(4-((((6-fluoroquinolin-2-yl)methyl)amino)methyl)piperidin-1-yl)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione was prepared using the General Reductive Amina-

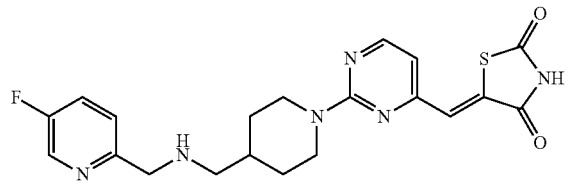
tion Procedure (Example 169) and 6-fluoroquinoline-2-carbaldehyde (32.7 mg, 45.5 mg theoretical, 71.9%). LC-MS m/z 479.5 (M+1).

Example 192



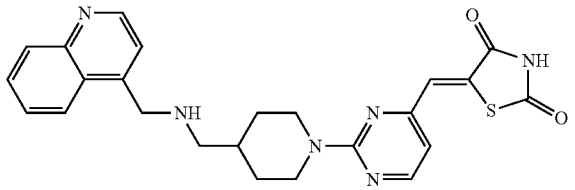
(Z)-5-((2-(4-((pyridin-2-ylamino)methyl)piperidin-1-yl) pyrimidin-4-yl)methylene)thiazolidine-2,4-dione was prepared using the General Reductive Amination Procedure (Example 169) and 2-chloroisonicotinaldehyde (19.6 mg, 42.3 mg theoretical, 46.4%). LC-MS m/z 445.5 (M+1).

Example 193



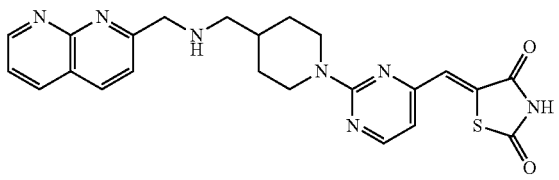
(Z)-5-((2-(4-((((5-fluoropyridin-2-yl)methyl)amino)methyl)piperidin-1-yl)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione was prepared using the General Reductive Amination Procedure (Example 169) and 5-fluoropicolinaldehyde (7.9 mg, 40.7 mg theoretical, 19.4%). LC-MS m/z 429.5 (M+1).

Example 194



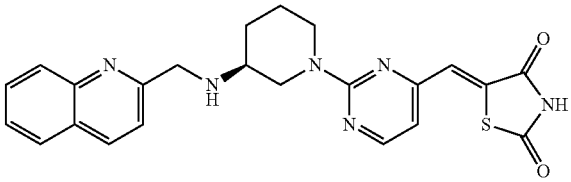
(Z)-5-((2-(4-(((quinolin-4-ylmethyl)amino)methyl)piperidin-1-yl)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione was prepared using the General Reductive Amination Procedure (Example 169) and quinoline-4-carbaldehyde (24.6 mg, 43.8 mg theoretical, 56.2%). LC-MS m/z 461.5 (M+1).

Example 195



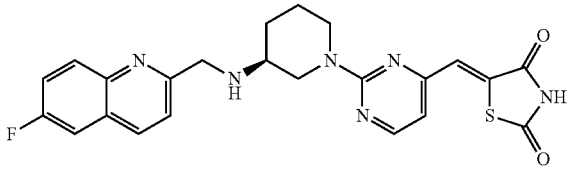
(Z)-5-((2-(4-((((1,8-naphthyridin-2-yl)methyl)amino)methyl)piperidin-1-yl)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione was prepared using the General Reductive Amination Procedure (Example 169) and 1,8-naphthyridine-2-carbaldehyde (6.9 mg, 43.8 mg theoretical, 15.7%). LC-MS m/z 462.5 (M+1).

Example 196



(S,Z)-5-((2-(3-((quinolin-2-ylmethyl)amino)piperidin-1-yl)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione was prepared using the General Reductive Amination Procedure (Example 169) and quinoline-2-carbaldehyde (30.9 mg, 54.9 mg theoretical, 56.3%). LC-MS m/z 447.2 (M+1).

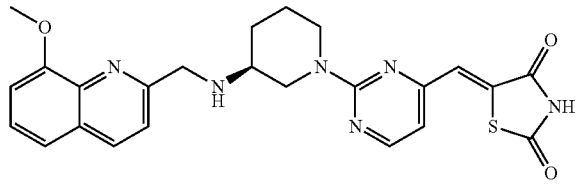
Example 197



(S,Z)-5-((2-(3-(((6-fluoroquinolin-2-yl)methyl)amino)piperidin-1-yl)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione was prepared using the General Reductive Amination

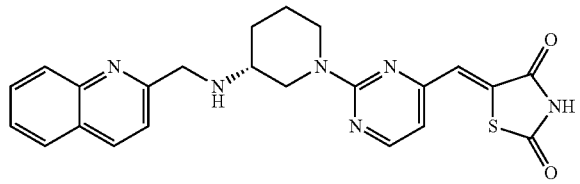
Procedure (Example 169) and 6-fluoroquinoline-2-carbaldehyde (26.7 mg, 57.1 mg theoretical, 46.7%). LC-MS m/z 465.5 (M+1).

Example 198



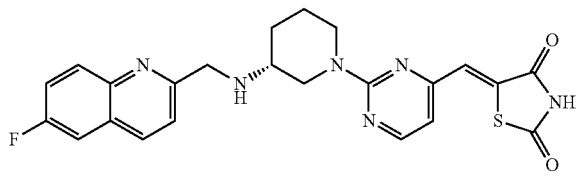
(S,Z)-5-((2-(3-(((8-methoxyquinolin-2-yl)methyl)amino)piperidin-1-yl)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione was prepared using the General Reductive Amination Procedure (Example 169) and 8-methoxyquinoline-2-carbaldehyde (16.4 mg, 58.6 mg theoretical, 28%). LC-MS m/z 477.5 (M+1).

Example 199



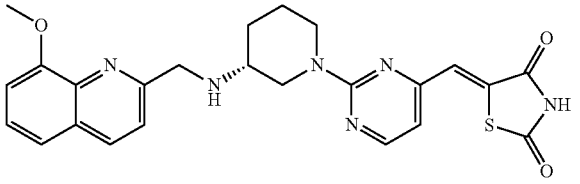
(R,Z)-5-((2-(3-((quinolin-2-ylmethyl)amino)piperidin-1-yl)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione was prepared using the General Reductive Amination Procedure (Example 169)e and quinoline-2-carbaldehyde (24.9 mg, 54.9 mg theoretical, 45.3%). LC-MS m/z 447.5 (M+1).

Example 200



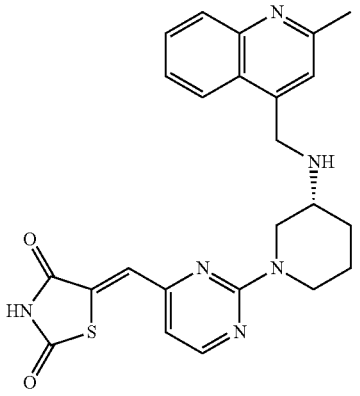
(R,Z)-5-((2-(3-((((6-fluoroquinolin-2-yl)methyl)amino)piperidin-1-yl)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione was prepared using the General Reductive Amination Procedure (Example 169) and 6-fluoroquinoline-2-carbaldehyde (24.1 mg, 57.1 mg theoretical, 42.2%). LC-MS m/z 465.5 (M+1).

Example 201



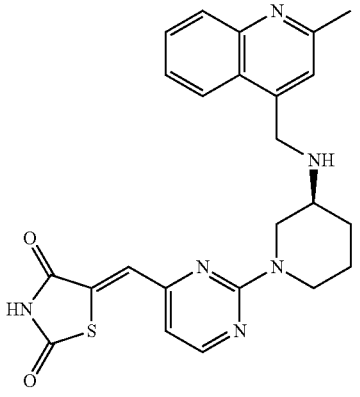
(R,Z)-5-((2-(3-(((8-methoxyquinolin-2-yl)methyl)amino)piperidin-1-yl)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione was prepared using the General Reductive Amination Procedure (Example 169) and 8-methoxyquinoline-2-carbaldehyde (15.5 mg, 58.6 mg theoretical, 26.4%). LC-MS m/z 477.5 (M+1).

Example 202



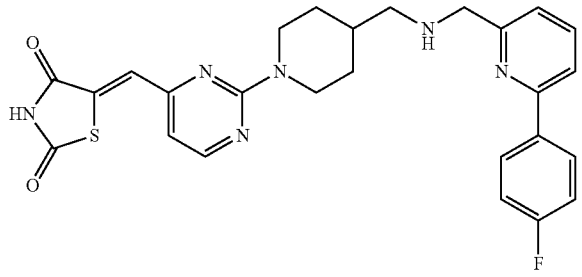
(R,Z)-5-((2-(3-(((2-methylquinolin-4-yl)methyl)amino)piperidin-1-yl)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione was prepared using the General Reductive Amination Procedure (Example 169) and 2-methylquinoline-4-carbaldehyde (25 mg, 56.6 mg theoretical, 44.1%). LC-MS m/z 461.5 (M+1).

Example 203



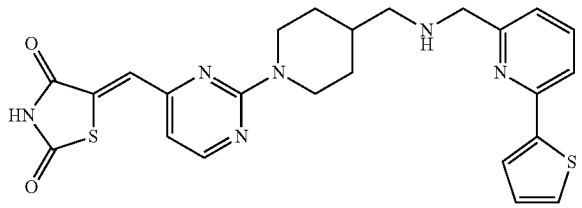
(S,Z)-5-((2-(3-(((2-methylquinolin-4-yl)methyl)amino) piperidin-1-yl)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione was prepared using the General Reductive Amination Procedure (Example 169) and 2-methylquinoline-4-carbaldehyde (30 mg, 56.6 mg theoretical, 53%). LC-MS m/z 461.5 (M+1).

Example 204



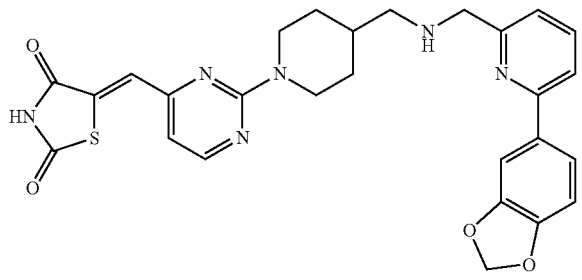
(Z)-5-((2-(4-((((6-(4-fluorophenyl)pyridin-2-yl)methyl) amino)methyl)piperidin-1-yl)pyrimidin-4-yl)methylene) thiazolidine-2,4-dione was prepared using the General Reductive Amination Procedure (Example 169) and 6-(4-fluorophenyl)picolinaldehyde (26.5 mg, 36.3 mg theoretical, 72.9%). LC-MS m/z 505.5 (M+1).

Example 205



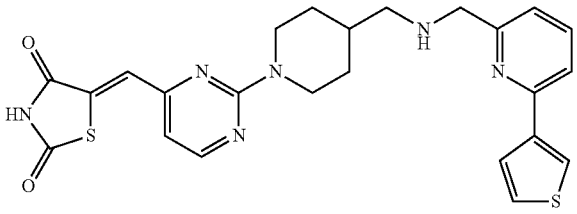
(Z)-5-((2-(4-((((6-(thiophen-2-yl)pyridin-2-yl)methyl) amino)methyl)piperidin-1-yl)pyrimidin-4-yl)methylene) thiazolidine-2,4-dione was prepared using the General Reductive Amination Procedure (Example 169) and 6-(thiophen-2-yl)picolinaldehyde (15.2 mg, 35.5 mg theoretical, 42.9%). LC-MS m/z 493.5 (M+1).

Example 206



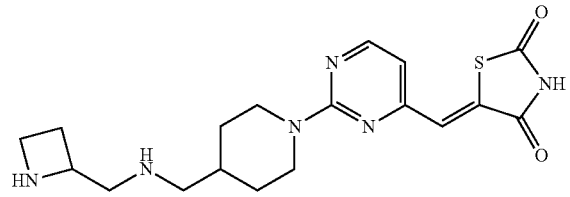
(Z)-5-((2-(4-((((6-(benzo[d][1,3]dioxol-5-yl)pyridin-2-yl)methyl)amino)methyl)piperidin-1-yl)pyrimidin-4- yl)methylene)thiazolidine-2,4-dione was prepared using the General Reductive Amination Procedure (Example 169) and 6-(benzo[d][1,3]dioxol-5-yl)picolinaldehyde (25.8 mg, 38.2 mg theoretical, 67.5%). LC-MS m/z 531.5 (M+1).

Example 207



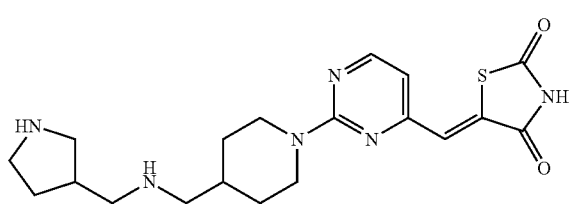
(Z)-5-((2-(4-((((6-(thiophen-3-yl)pyridin-2-yl)methyl) amino)methyl)piperidin-1-yl)pyrimidin-4-yl)methylene) thiazolidine-2,4-dione was prepared using the General Reductive Amination Procedure (Example 169) and 6-(thiophen-3-yl)picolinaldehyde (32.5 mg, 35.5 mg theoretical, 92%). LC-MS m/z 493.5 (M+1).

Example 208



(Z)-5-((2-(4-(((azetidin-2-ylmethyl)amino)methyl)piperidin-1-yl)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione was prepared using the General Reductive Amination Procedure (Example 169) and tert-butyl 2-formylazetidine-1-carboxylate followed by the general TFA de-protection procedure (15.2 mg, 68 mg theoretical, 22.4%). LC-MS m/z 389.5 (M+1).

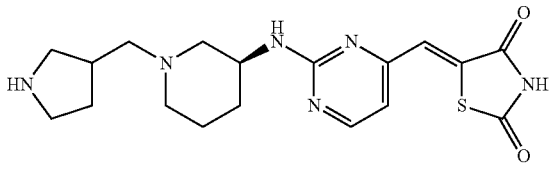
Example 209



(Z)-5-((2-(4-(((pyrrolidin-3-ylmethyl)amino)methyl)piperidin-1-yl)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione was prepared using the General Reductive Amination Procedure (Example 169) and tert-butyl 3-formylpyrrolidine-

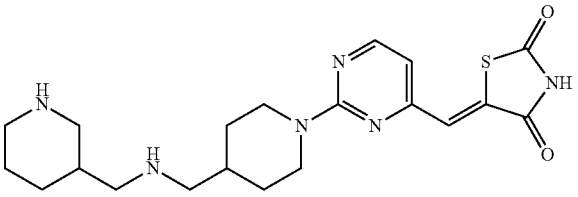
1-carboxylate followed by the general TFA de-protection procedure (17.1 mg, 70.4 mg theoretical, 24%). LC-MS m/z 403.5 (M+1).

Example 210



(Z)-5-((2-(((3S)-1-(pyrrolidin-3-ylmethyl)piperidin-3-yl) amino)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione was prepared using the General Reductive Amination Procedure (Example 169) and tert-butyl 3-formylpyrrolidine-1-carboxylate followed by the general TFA de-protection procedure (2.7 mg, 34.0 mg theoretical, 7.9%). LC-MS m/z 389.2 (M+1).

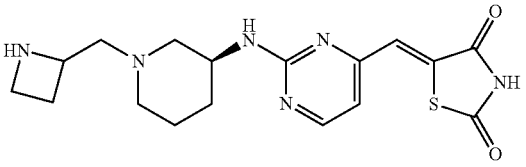
Example 211



(Z)-5-((2-(4-(((piperidin-3-ylmethyl)amino)methyl)piperidin-1-yl)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione was prepared using the General Reductive Amination

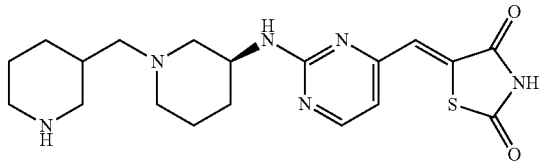
Procedure (Example 169) and tert-butyl 3-formylpiperidine-1-carboxylate followed by the general TFA de-protection procedure (26.5 mg, 72.9 mg theoretical, 36.4%). LC-MS m/z 417.2 (M+1).

Example 212



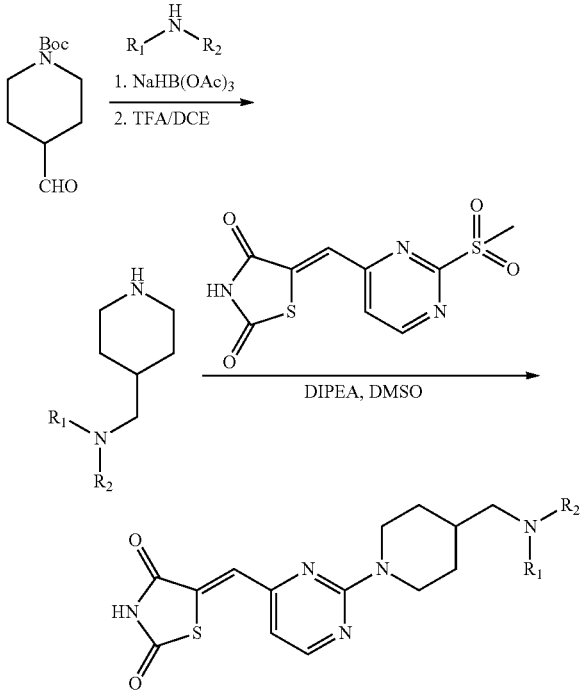
(Z)-5-((2-(((3S)-1-(azetidin-2-ylmethyl)piperidin-3-yl) amino)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione was prepared using the General Reductive Amination Procedure (Example 169) and tert-butyl 2-formylazetidine-1-carboxylate followed by the general TFA de-protection procedure (2.2 mg, 32.8 mg theoretical, 6.0%). LC-MS m/z 375.2 (M+1).

Example 213



(Z)-5-((2-(((3S)-1-(piperidin-3-ylmethyl)piperidin-3-yl) amino)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione was prepared using the General Reductive Amination Procedure (Example 169) and tert-butyl 3-formylpiperidine-1-carboxylate followed by the general TFA de-protection procedure (4.5 mg, 35.3 mg theoretical, 11.9%). LC-MS m/z 403.2 (M+1).

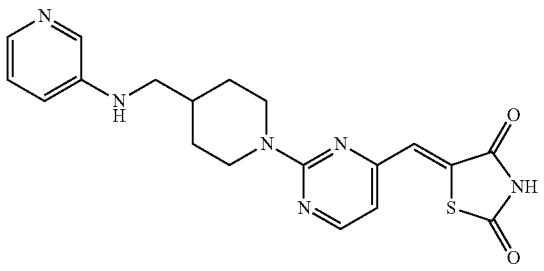
Example 214



General Reverse Reductive Amination Procedure: A 2-dram round-bottomed vial was charged with tert-butyl 4-formylpiperidine-1-carboxylate (0.7 mmol), the amine (1 equiv., 0.7 mmol), DCE (3 mL), and shaken for 1 h at RT. The reaction mixture was then treated with $NaBH(OAc)_3$ (2 equiv., 1.4 mmol) and shaken for 16 h at RT. The reaction mixture was then washed with saturated $NaHCO_3$ (3 mL) and the aqueous layer was back extracted with DCE (2×2 mL. The combined organic layer was concentrated under reduced pressure (GeneVac HT-4) and the crude residue was purified by HPLC using a $MeOH/H_2O$ gradient with TFA as the modifier. The resulting Boc-protected piperidine analog was

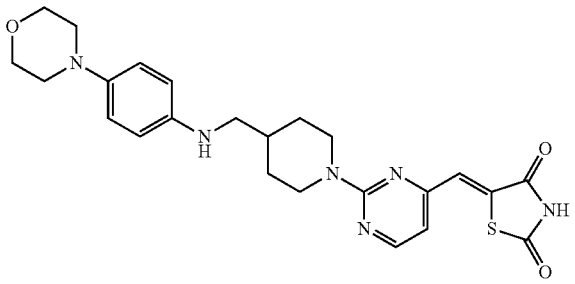
treated with DCE (3 mL), TFA (0.5 mL), and shaken at RT for 2 h. The reaction mixture was concentrated under reduced pressure (GeneVac HT-4) and used in the general displacement procedure without further purification.

Example 215



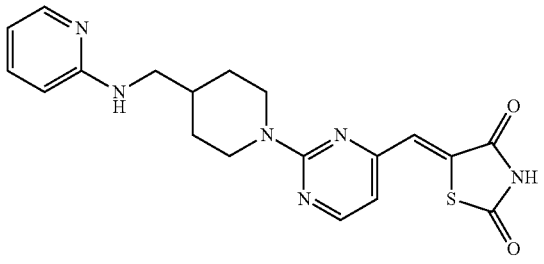
(Z)-5-((2-(4-((pyridin-3-ylamino)methyl)piperidin-1-yl) pyrimidin-4-yl)methylene)thiazolidine-2,4-dione was prepared using the General Reverse Reductive Amination Procedure (Example 214) and pyridin-3-amine (15.5 mg, 41.7 mg theoretical, 37.2%). LC-MS m/z 397.5 (M+1).

Example 216



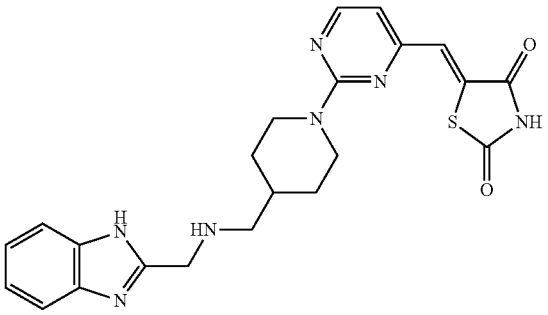
(Z)-5-((2-(4-(((4-morpholinophenyl)amino)methyl)piperidin-1-yl)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione was prepared using the General Reverse Reductive Amination Procedure (Example 214) and 4-morpholinoaniline (12.5 mg, 50.5 mg theoretical, 24.7%). LC-MS m/z 481.5 (M+1).

Example 217



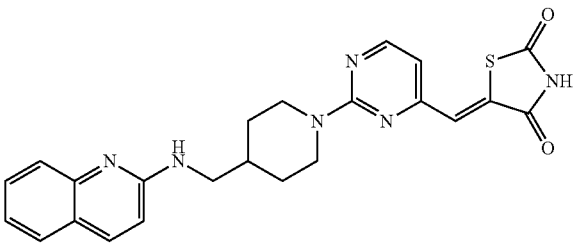
(Z)-5-((2-(4-((pyridin-2-ylamino)methyl)piperidin-1-yl) pyrimidin-4-yl)methylene)thiazolidine-2,4-dione was prepared using the General Reverse Reductive Amination Procedure (Example 214) and pyridin-2-amine (21.2 mg, 41.7 mg theoretical, 50.9%). LC-MS m/z 397.5 (M+1).

Example 218



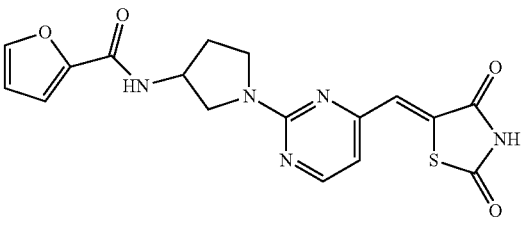
(Z)-5-((2-(4-((((1H-benzo[d]imidazol-2-yl)methyl) amino)methyl)piperidin-1-yl)pyrimidin-4-yl)methylene) thiazolidine-2,4-dione was prepared using the General Reverse Reductive Amination Procedure (Example 214) and (1H-benzo[d]imidazol-2-yl)methanamine (8 mg, 42.7 mg theoretical, 18.7%). LC-MS m/z 450.5 (M+1).

Example 219



(Z)-5-((2-(4-((quinolin-2-ylamino)methyl)piperidin-1-yl) pyrimidin-4-yl)methylene)thiazolidine-2,4-dione was prepared using the General Reverse Reductive Amination Procedure (Example 214) and quinolin-2-amine (21.2 mg, 128 mg theoretical, 16.53%). LC-MS m/z 447.5 (M+1).

Example 220

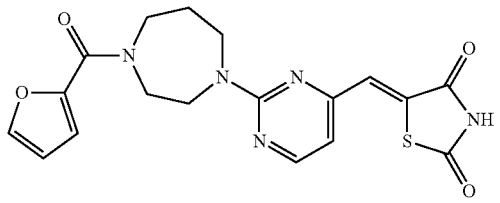


(Z)-N-(1-(4-((2,4-dioxothiazolidin-5-ylidene)methyl)pyrimidin-2-yl)pyrrolidin-3-yl)furan-2-carboxamide was prepared as follows.

A 2-dram round-bottomed vial was charged with (Z)-5-(2-(3-aminopyrrolidin-1-yl)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione, prepared using the general displacement pro-

cedure followed by the general TFA de-protection procedure, (25 mg, 0.065 mmol), DCM (1 mL), furan-2-carbonyl chloride (8 μL, 0.082 mmol, 1.3 equiv.), and pyridine (0.040 mL, 0.491 mmol, 7.5 equiv.). The reaction mixture was shaken at RT for 16 h, the solvent was removed under reduced pressure (Genevac HT-4), and the crude residue was purified using reverse phase HPLC (MS-triggered fraction collection) with an acetonitrile/water gradient and trifluoroacetic acid as the modifier. The pure fractions were then concentrated under reduced pressure (Genevac HT-4) to provide the title compound (2.7 mg, 33.1 mg theoretical, 8.2%). LC-MS m/z 386.1 (M+1).

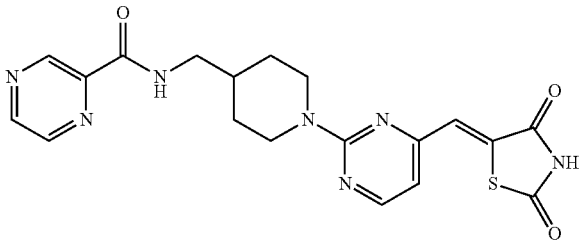
Example 221



(Z)-5-((2-(4-(furan-2-carbonyl)-1,4-diazepan-1-yl)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione was prepared as follows.

A 2-dram round-bottomed vial was charged with (Z)-5-((2-(1,4-diazepan-1-yl)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione, prepared using the general displacement procedure followed by the general TFA de-protection procedure, (25 mg, 0.062 mmol), DCM (1 mL), furan-2-carbonyl chloride (8.07 μL, 0.062 mmol, 1 equiv.), and pyridine (0.040 mL, 0.491 mmol, 8 equiv.). The reaction mixture was shaken at RT for 16 h, the solvent was removed under reduced pressure (Genevac HT-4), and the crude residue was purified using reverse phase HPLC (MS-triggered fraction collection) with an acetonitrile/water gradient and trifluoroacetic acid as the modifier. The pure fractions were then concentrated under reduced pressure (Genevac HT-4) to provide the title compound (1.9 mg, 32.7 mg theoretical, 5.8%). LC-MS m/z 400.1 (M+1).

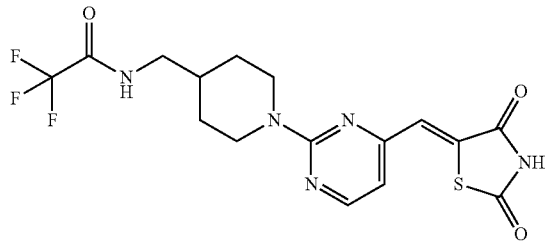
Example 222



(Z)-N-((1-(4-((2,4-dioxothiazolidin-5-ylidene)methyl)pyrimidin-2-yl)piperidin-4-yl)methyl)pyrazine-2-carboxamide was prepared as follows.

A 2-dram round-bottomed vial was charged with (Z)-5-(2-(4-(aminomethyl)piperidin-1-yl)pyrimidin-4-yl)methylene) thiazolidine-2,4-dione, prepared using the general displacement procedure followed by the general TFA de-protection procedure, (56 mg, 0.175 mmol), DCM (3 mL), pyrazine-2-carbonyl chloride (25 mg, 0.175 mmol, 1 equiv.), and pyridine (0.120 mL, 1.47 mmol, 8.4 equiv.). The reaction mixture was shaken at RT for 16 h, the solvent was removed under reduced pressure (Genevac HT-4), and the crude residue was purified using reverse phase HPLC (MS-triggered fraction collection) with an acetonitrile/water gradient and trifluoroacetic acid as the modifier. The pure fractions were then concentrated under reduced pressure (Genevac HT-4) to provide the title compound (4.9 mg, 74.5 mg theoretical, 6.6%). LC-MS m/z 426.5 (M+1).

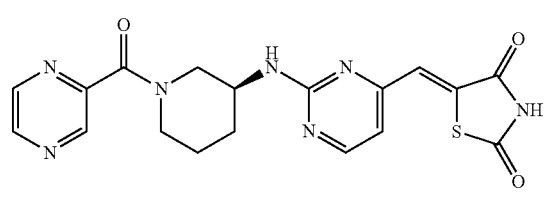
Example 223



(Z)-N-((1-(4-((2,4-dioxothiazolidin-5-ylidene)methyl)pyrimidin-2-yl)piperidin-4-yl)methyl)-2,2,2-trifluoroacetamide was prepared as follows.

A 2-dram round-bottomed vial was charged with (Z)-5-(2-(4-(aminomethyl)piperidin-1-yl)pyrimidin-4-yl)methylene) thiazolidine-2,4-dione, prepared using the general displacement procedure followed by the general TFA de-protection procedure, (56 mg, 0.175 mmol), DCM (3 mL), 2,2,2-trifluoroacetyl chloride (23 mg, 0.175 mmol, 1 equiv.), and pyridine (0.120 mL, 1.47 mmol, 8.4 equiv.). The reaction mixture was shaken at RT for 16 h, the solvent was removed under reduced pressure (Genevac HT-4), and the crude residue was purified using reverse phase HPLC (MS-triggered fraction collection) with an acetonitrile/water gradient and trifluoroacetic acid as the modifier. The pure fractions were then concentrated under reduced pressure (Genevac HT-4) to provide the title compound (6.5 mg, 72.7 mg theoretical, 8.9%). LC-MS m/z 416.1 (M+1).

Example 224

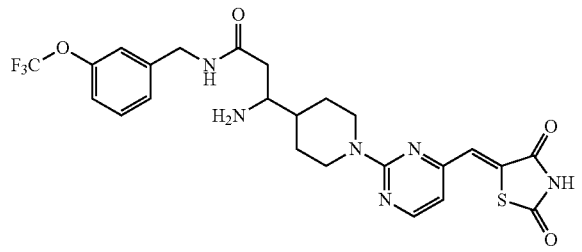


(S,Z)-5-((2-((1-(pyrazine-2-carbonyl)piperidin-3-yl) amino)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione was prepared as follows.

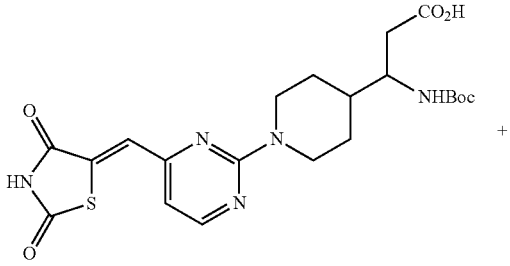
A 2-dram round-bottomed vial was charged with (S,Z)-5-((2-(piperidin-3-ylamino)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione, prepared using the general displacement procedure followed by the general TFA de-protection procedure, (27 mg, 0.088 mmol), DCM (2 mL), pyrazine-2-carbonyl chloride (12.5 mg, 0.088 mmol, 1 equiv.), and pyridine (0.080 mL, 0.982 mmol, 11 equiv.). The reaction mixture was shaken at RT for 16 h, the solvent was removed under reduced pressure (Genevac HT-4), and the crude residue was purified using reverse phase HPLC (MS-triggered fraction collection) with an acetonitrile/water gradient and trifluoroacetic acid as

the modifier. The pure fractions were then concentrated under reduced pressure (Genevac HT-4) to provide the title compound (2.6 mg, 36.1 mg theoretical, 6.4%). LC-MS m/z 412.1 (M+1).

Example 225



(Z)-3-amino-3-(1-(4-((2,4-dioxothiazolidin-5-ylidene) methyl)pyrimidin-2-yl)piperidin-4-yl)-N-(3-(trifluoromethoxy)benzyl)propanamide was prepared as follows.



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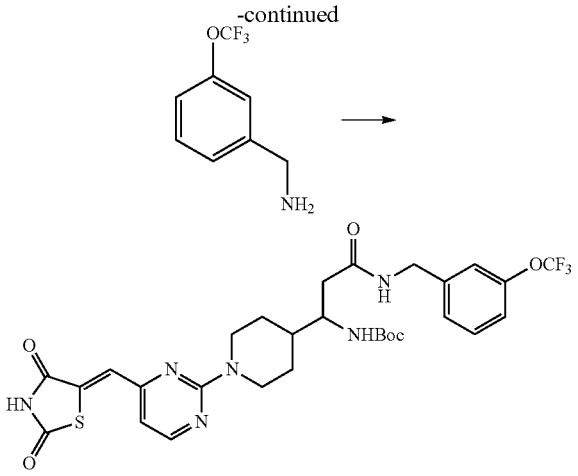
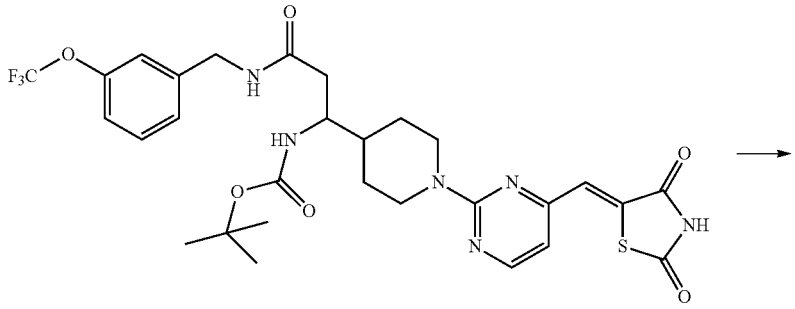
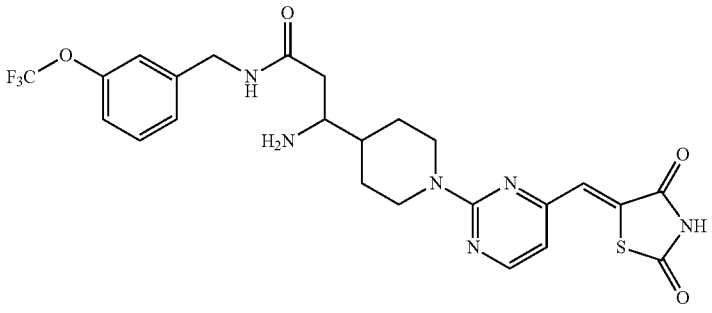


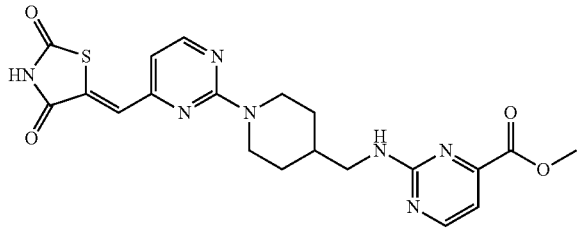
A 2-dram round-bottomed vial was charged with (Z)-3-((tert-butoxycarbonyl)amino)-3-(1-(4-((2,4-dioxothiazolidin-5-ylidene)methyl)pyrimidin-2-yl)piperidin-4-yl)propanoic acid, prepared using the general displacement procedure, (25 mg, 0.052 mmol), DMF (1 mL), DIPEA (34.9 μL, 0.209 mmol, 4 equiv.), and (3-(trifluoromethoxy)phenyl) methanamine (7.85 μL, 0.052 mmol, 1 equiv.). The reaction mixture was shaken for 20 minutes then HBTU (29.8 mg, 0.079 mmol, 1.5 equiv.) was added and the reaction mixture was shaken at RT for 3 h. The solvent was removed under reduced pressure (Genevac HT-4) and the resulting solid was washed with water (2×1 mL) and dried under high vacuum to provide 20 mg of (Z)-tert-butyl (1-(1-(4-((2,4-dioxothiazolidin-5-ylidene)methyl)pyrimidin-2-yl)piperidin-4-yl)-3-oxo-3-(3-(trifluoromethoxy)benzyl)amino)propyl)carbamate (20 mg, 34.1 mg theoretical, 58.7%).





A 2-dram round-bottomed vial was charged with (Z)-tert-butyl (1-(1-(4-(2,4-dioxothiazolidin-5-ylidene)methyl)pyrimidin-2-yl)piperidin-4-yl)-3-oxo-3-((3-(trifluoromethoxy) benzyl)amino)propyl)carbamate (20 mg, 0.031 mmol), DCM (0.5 mL), and TFA (0.5 mL). The reaction mixture was shaken at RT for 16 h. The solvent was removed under reduced pressure (Genevac HT-4) and the crude residue was purified using reverse phase HPLC (MS-triggered fraction collection) with an acetonitrile/water gradient and trifluoroacetic acid as the modifier. The pure fractions were then concentrated under reduced pressure (Genevac HT-4) to provide the title compound (15.6 mg, 16.9 mg theoretical, 92%). LC-MS m/z 551.2 (M+1)

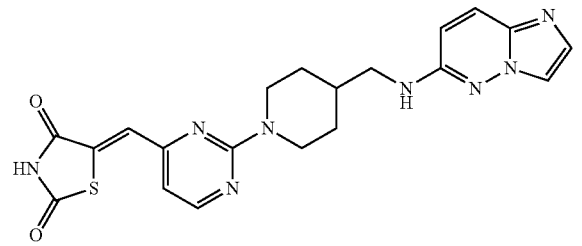
Example 226



(Z)-methyl 2-(((1-(4-((2,4-dioxothiazolidin-5-ylidene) methyl)pyrimidin-2-yl)piperidin-4-yl)methyl)amino)pyrimidine-4-carboxylate was prepared as follows.

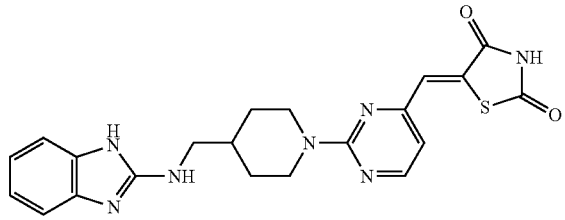
Methyl 2-((piperidin-4-ylmethyl)amino)pyrimidine-4-carboxylate was prepared as follows: A 40 mL round-bottomed vial was charged with tert-butyl 4-(aminomethyl)piperidine-1-carboxylate (1.76 mmol, 1.1 equiv.), acetonitrile (4 mL), DiPEA (2.37 mmol, 1.5 equiv.), methyl 2,6-dichloropyrimidine-4-carboxylate (1.58 mmol, 1 equiv.), and then shaken at 85° C. for 72 h. The reaction mixture was concentrated under reduced pressure and purified on SiO_2 using a Biotage and a 10-50% EtOAc/hexanes gradient to provide the desired protected amine (233 mg, 552 mg theoretical, 42%). Methyl 2-((piperidin-4-ylmethyl)amino)pyrimidine-4-carboxylate was prepared using the general TFA de-protection procedure and used directly in the general displacement procedure to provide the title compound (4 mg, 73.4 mg theoretical, 5%). LC-MS m/z 456.1 (M+1).

Example 227



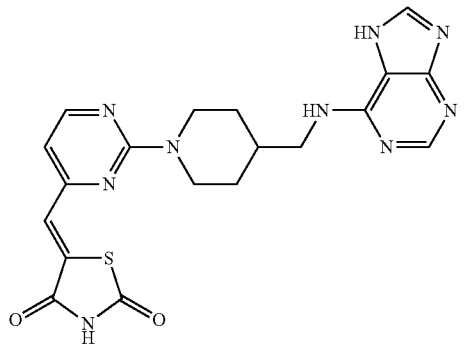
(Z)-5-((2-(4-((imidazo[1,2-b]pyridazin-6-ylamino)methyl)piperidin-1-yl)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione was prepared using a procedure similar to the procedure used in the synthesis of Example 226 to provide the title compound (12.2 mg, 45.9 mg theoretical, 26.6%). LC-MS m/z 437.5 (M+1).

Example 228



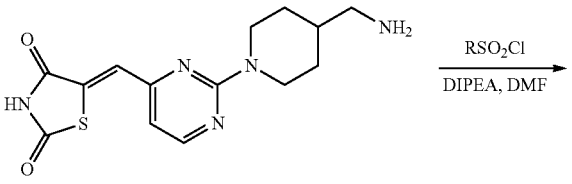
(Z)-5-((2-(4-(((1H-benzo[d]imidazol-2-yl)amino)methyl) piperidin-1-yl)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione was prepared using a procedure similar to the procedure used in the synthesis of Example 226 to provide the title compound (21.4 mg, 45.8 mg theoretical, 46.7%). LC-MS m/z 436.5 (M+1).

Example 229

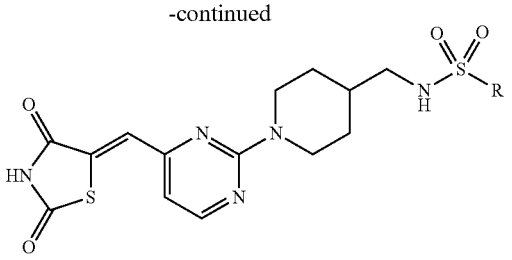


(Z)-5-((2-(4-(((7H-purin-6-yl)amino)methyl)piperidin-1-yl)pyrimidin-4-yl)methylene)thiazolidine-2,4-dione was prepared using a procedure similar to the procedure used in the synthesis of Example 226 to provide the title compound (12.7 mg, 41.6 mg theoretical, 30.6%). LC-MS m/z 438.5 (M+1).

Example 230

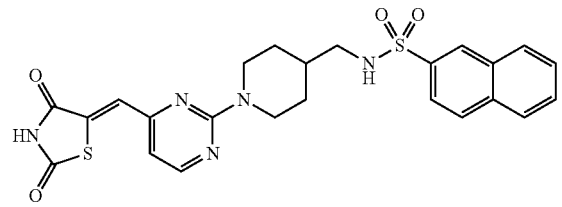


-continued



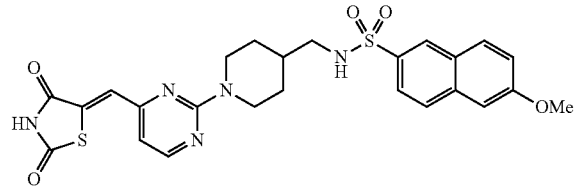
General Procedure for the Preparation of Sulfonamides A 2-dram round-bottomed vial was charged with the appropriate sulfonyl chloride (0.072 mmol, 1 equiv.) in 0.5 mL of DMF, and then treated carefully with a solution of the appropriate amine intermediate, prepared using the general displacement procedure followed by the general TFA de-protection procedure, (0.072 mmol, 1 equiv.), DIPEA (0.288 mmol, 4 equiv.), and 1 mL of DMF. The reaction mixture was then shaken at room temperature overnight. The reaction mixture was partitioned between 2 mL DCE and 1 mL sat. $NaHCO_3$ and the aqueous layer was extracted with DCE (2×2 mL). The combined organic layer was the concentrated under reduced pressure (Genevac HT-4) and the crude residue was purified using reverse phase HPLC (MS-triggered fraction collection) with an acetonitrile/water or methanol/water gradient and trifluoroacetic acid as the modifier. The pure fractions were then concentrated under reduced pressure (Genevac HT-4) to afford the sulfonamide analogs.

Example 231



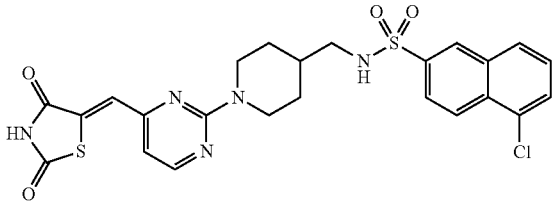
(Z)-N-((1-(4-((2,4-dioxothiazolidin-5-ylidene)methyl)pyrimidin-2-yl)piperidin-4-yl)methyl)naphthalene-2-sulfonamide was prepared using a procedure similar to the general procedure described in Example 230 to provide the title compound (7.7 mg, 36.7 mg theoretical, 21%). LC-MS m/z 510.5 (M+1).

Example 232



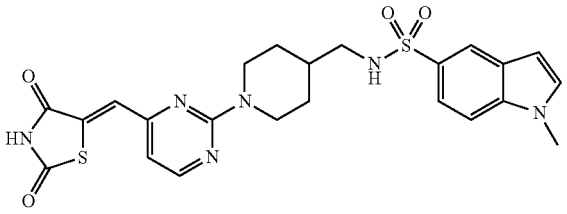
(Z)-N-((1-(4-((2,4-dioxothiazolidin-5-ylidene)methyl)pyrimidin-2-yl)piperidin-4-yl)methyl)-6-methoxynaphthalene-2-sulfonamide was prepared using a procedure similar to the general procedure described in Example 230 to provide the title compound (15.2 mg, 38.9 mg theoretical, 39.1%). LC-MS m/z 540.5 (M+1).

Example 233



(Z)-5-chloro-N-((1-(4-((2,4-dioxothiazolidin-5-ylidene)methyl)pyrimidin-2-yl)piperidin-4-yl)methyl)naphthalene-2-sulfonamide was prepared using a procedure similar to the general procedure described in Example 230 to provide the title compound (9.2 mg, 39.2 mg theoretical, 23.5%). LC-MS m/z 545 (M+1).

Example 234



(Z)-N-((1-(4-((2,4-dioxothiazolidin-5-ylidene)methyl)pyrimidin-2-yl)piperidin-4-yl)methyl)-1-methyl-1H-indole-5-sulfonamide was prepared using a procedure similar to the general procedure described in Example 230 to provide the title compound (13.2 mg, 36.9 mg theoretical, 35.8%). LC-MS m/z 513.5 (M+1).

Example 235

Protocols for Kinase Activity Screening for CK1γ1(h), CK1γ2(h), CK1γ3(h), CK1δ(h) and CK1(y): Kinase screening was performed by Millipore UK Ltd. Kinase dilution buffer composition: 20 mM MOPS, 1 mM EDTA, 0.01% Brij-35, 5% Glycerol, 0.1% b-mercaptoethanol, 1 mg/mL BSA.

TABLE 4

Kinase assay ATP concentration within 15 μM of K_M.

Kinase	K_M (μM)
CK1γ1(h)	15
CK1γ2(h)	10
CK1γ3(h)	10
CK1δ(h)	70
CK1(y)	45

In a final reaction volume of 25 μL, the compound of interest (at the desired concentration) and the appropriate kinase (5-10 mU) were incubated with 8 mM MOPS pH 7.0,

0.2 mM EDTA, 200 μM KRRRALS(p)VASLPGL (SEQ ID NO:1), 10 mM magnesium acetate and [γ-^{33}P-ATP] (specific activity approx. 500 cpm/pmol, concentration as required). The reaction was initiated by the addition of the MgATP mix. After incubation for 40 minutes at room temperature, the reaction was stopped by the addition of 5 μL of a 3% phosphoric acid solution. 10 μL of the reaction mixture was then spotted onto a P30 filtermat; and washed three times for 5 minutes in 75 mM phosphoric acid, and once in methanol prior to drying and scintillation counting. The estimated IC_{50} values for several compounds are provided in Table 5.

TABLE 5

Estimated IC_{50} values

Compound	Kinase	IC_{50} (nM)
4981	CK1γ1(h)	121
4981	CK1γ2(h)	19
4981	CK1γ3(h)	401
4981	CK1δ(h)	>10,000
4981	CK1(y)	>10,000
4993	CK1γ1(h)	5,034
4993	CK1γ2(h)	716
4993	CK1γ3(h)	3,168
4993	CK1δ(h)	>10,000
4993	CK1(y)	9,853
4991	CK1γ1(h)	571
4991	CK1γ2(h)	146
4991	CK1γ3(h)	1,085
4991	CK1δ(h)	>10,000
4991	CK1(y)	1,161
4999	CK1γ1(h)	163
4999	CK1γ2(h)	37
4999	CK1γ3(h)	470
4999	CK1δ(h)	3,446
4999	CK1(y)	2,990
4985	CK1γ1(h)	2,568
4985	CK1γ2(h)	191
4985	CK1γ3(h)	4,714
4985	CK1δ(h)	>10,000
4985	CK1(y)	3,717
4992	CK1γ1(h)	4,543
4992	CK1γ2(h)	745
4992	CK1γ3(h)	1,736
4992	CK1δ(h)	>10,000
4992	CK1(y)	1,760
4996	CK1γ1(h)	624
4996	CK1γ2(h)	27
4996	CK1γ3(h)	>10,000
4996	CK1δ(h)	>10,000
4996	CK1(y)	2,447
5000	CK1γ1(h)	4,036
5000	CK1γ2(h)	2,367
5000	CK1γ3(h)	3,498
5000	CK1δ(h)	9,153
5000	CK1(y)	1,719

The relative activity of the kinase as a function of the concentration of the compounds are depicted in FIGS. **1-40**.

Additional IC_{50}s for CK1 are shown in Table 6:

TABLE 6

CK1 IC_{50} values (nM)

ID	CK1γ1	CK1γ2 IC_{50}	CK1γ3
10189		645	
10190		519	
10196		63	
10197		12	
10202	529	102	700
10204		110	

TABLE 6-continued

CK1 IC_{50} values (nM)

ID	CK1γ1	CK1γ2 IC_{50}	CK1γ3
10205	127	38	131
10206	1254	77	566
10216		48	

Additional % activity data is shown in Table 7.

TABLE 7

% Activity for various compounds

ID	CK1γ1	CK1γ2	CK1γ3
10190	80	33	94
10204	14	7	31
10191	85	72	85
10205	15	2	8
10192	108	104	96
10206	43	13	37
10193	97	94	93
10209	104	79	96
10194	92	79	78
10211	91	84	79
10196	57	15	31
10212	99	99	99
10183	86	85	74
10197	14	−2	30
10214	98	100	95
10200	82	59	77
10215	107	101	96
10202	38	15	38
10216	18	1	31
10189	64	44	67
10203	78	71	80
10217	104	93	90

Example 236

PIM kinase assays were performed by Millipore UK Ltd. IC_{50} data is summarized in Table 8, and percent activity data is summarized in Table 9.

TABLE 8

PIM kinase IC_{50} values

ID	Pim1 IC_{50} (nM)	Pim2 IC_{50} (nM)	Pim3 IC_{50} (nM)
4981	6348	1371	
4991	1775	555	
4980	5320	665	
4982	287	256	
4983	4328	3080	
4989	4492	2051	
4992	784	392	
4993	189	91	191
4994	1578	786	
4995	1819	2297	
4998	4107	2741	
5000	143	155	187
5117	3400	8996	
10183	1332	730	
10212	304	477	
10214			
10216	499	163	
10209	574	350	
10202	857	108	
10189	2966	690	
10200	3226	714	
10190	3978	715	
10191	2110	1310	
10192	1655	2438	

TABLE 8-continued

PIM kinase IC_{50} values			
ID	Pim1 IC_{50} (nM)	Pim2 IC_{50} (nM)	Pim3 IC_{50} (nM)
10193	2739	3846	
10194	4399	2072	
10206	3124	2217	
10257	51	20	13
10256	45	47	27

TABLE 9

PIM kinase percent activity at varying concentrations

	% activity 10 microM		% activity 1 microM			% activity 10 microM		
ID	PIM 1	PIM 2	PIM 1	PIM 2	PIM 3	PIM 1	PIM 2	PIM 3
4848	37	34						
4980	19	6						
4982	2	8						
4983	26	24						
4985	30	23						
4987	38	11						
4989	23	19						
4992	4	11						
4993	0	9						
4994	3	5						
4995	14	20						
4996	10	27						
4997	18	11						
4998	22	16						
4999	27	10						
5000	19	4						
5001	17	16						
5113	86	54						
5117	10	22						
5121	105	61						
5126	39	15						
5132	86	61						
5114	113	87						
5118	92	50						
5122	94	69						
5127	61	67						
5133	50	35						
5115	77	63						
5119	97	79						
5124	88	59						
5128	108	64						
5116	106	86						
5120	95	62						
5125	83	49						
5131	117	83						
5336	103	90						
5337	104	82						
5338	117	103						
5339	75	70						
5340	98	78						
5345	113	85						
5349	101	94						
5353	109	101						
5358	89	81						
5341	107	109						
5346	89	97						
5350	76	97						
5354	87	91						
5343	76	80						
5347	87	105						
5351	93	96						
5355	50	52						
5344	95	103						
5348	83	92						
5352	99	103						
5357	100	101						
5359	94	99						

TABLE 9-continued

PIM kinase percent activity at varying concentrations

	% activity 10 microM		% activity 1 microM			% activity 10 microM		
ID	PIM 1	PIM 2	PIM 1	PIM 2	PIM 3	PIM 1	PIM 2	PIM 3
5376	94	108						
5382	80	101						
5363	86	84						
5378	88	92						
5369	84	122						
5379	81	107						
5371	102	110						
5380	93	114						
10178	84	122						
5134	51	44						
10179	63	81						
10180	49	69						
10181	74	93						
10182	59	44						
10183	8	7						
10184	90	115						
10185	24	20						
10227		88						
10244		134						
10247		121						
10248		121						
10249		122						
10211	44	41						
10212	5	6						
10214	51	44						
10215	19	24						
10216	8	21						
10217	100	102						
10209	11	8						
10202	10	1						
10189	14	4						
10200	15	6						
10190	16	9						
10191	22	13						
10192	23	25						
10193	20	24						
10194	23	18						
10196	65	80						
10197	39	38						
10203	35	52						
10204	35	23						
10205	50	23						
10206	18	17						
10257			8	8	2	18	12	3
10256			9	12	0	24	28	8
10265			8	21	31	33	57	57
10264			20	30	17	49	49	46
10262			23	33	17	51	62	40
10255			34	29	36	59	52	59
10259			57	72	48	80	97	67
10258			46	44	32	82	76	56
10251			67	38	51	84	64	66
10253			67	63	54	87	81	79
10250			53	28	27	90	63	83
10263			78	82	92	91	91	85
10260			50	63	33	94	79	60

TABLE 9-continued

PIM kinase percent activity at varying concentrations								
	% activity 10 microM		% activity 1 microM			% activity 10 microM		
ID	PIM 1	PIM 2	PIM 1	PIM 2	PIM 3	PIM 1	PIM 2	PIM 3
10252			65	54	38	96	83	70
10254			72	68	37	96	88	73
10261			82	99	62	100	117	87

Additional percent activity data at 10 micromolar (μM) for compounds 4981 and 4991 is depicted in Tables 10 and 11.

TABLE 10

% Activity at 10 μM.					
ID	GSK3β(h)	Pim-1(h)	Pim-2(h)	Pim-3(h)	VRK2(h)
4981	93	50	29	57	103
4991	66	20	15	73	103

TABLE 11

PI3 Kinase	4981	4991
PI3 (p110β/p85α)(h)	99	88
PI3 (p120γ)(h)	85	61
PI3 (p110δ/p85α)(h)	86	45
PI3 (p110α/p85α)(m)	83	46
PI3 (p110β/p65α)(m)	84	46
PI3 (p110α(E545K)/p85α)(m)	75	51
PI3 (p110α(H1047R)/p85α)(m)	76	22
PI3 (p110β/p85β)(m)	99	86
PI3 (p110β/p85α)(m)	95	85
PI3 (p110δ/p85α)(m)	85	57
PI3 (p110α(E542K))/p85α)(h)	82	52
PI3 KC2 α(h)	90	84

Example 237

Cell Proliferation Studies

Inhibition of PC-3 Cells:

Cells: PC-3 cells, ATCC Passage unknown, Mycoplasma free.

Medium: DMEM Medium (GIBCO Cat#11995073) supplemented with 10% fetal bovine serum (Hyclone Cat#SH30396.03).

Seeding: 3,000 cells/well (100 μL) into 96-well plates, incubated overnight at 37° C. in a humidified 5% CO_2 atmosphere.

Treatment: Test compounds were first diluted 333-fold in the medium. Fifty microliters (50 μL) of diluted compounds were added into each well (i.e., another 3-fold dilution). The final concentration of test compounds was 10 μM. The final concentrations of the positive control (Gemcitabine, also 50 μL added in each well) is shown in FIG. **41**. The cells were incubated for 72 hours after addition of the test compounds.

MTS: Added 20 μL of MTS solution (Promega Cat #G5430) into each well and incubated for 4 hours.

Calculation: % of inhibition+(AVE zero ctrl−AVE compound)/AVE zero ctrl*100.

Results are shown in Table 12:

TABLE 12

Compound ID	Test No.	OD value			Color control	Real OD			Avg.	Inhibition Rate %
4981	1	2.004	2.010	1.893	0.676	1.329	1.334	1.218	1.294	0.8
4985	2	1.876	1.934	1.891	0.595	1.280	1.339	1.296	1.305	−0.1
4991	3	1.804	1.851	1.775	0.599	1.205	1.252	1.176	1.211	7.1
4999	4	1.846	1.911	1.824	0.590	1.256	1.321	1.234	1.270	2.6
Con	—	1.679	2.079	1.915	0.587	1.092	1.492	1.328	1.304	0.0
	1.2 μM	1.783	1.800	1.833	0.587	1.196	1.213	1.245	1.218	6.5
	3.7 μM	1.769	1.800	1.841	0.587	1.182	1.213	1.253	1.216	6.7
	11.1 μM	1.558	1.625	1.670	0.587	0.971	1.038	1.083	1.031	20.9
	33.3 μM	1.311	1.231	1.277	0.587	0.724	0.644	0.689	0.686	47.4
	100 μM	1.145	1.163	1.186	0.587	0.558	0.576	0.598	0.577	55.7
	300 μM	0.805	0.925	0.833	0.587	0.218	0.338	0.245	0.267	79.5

Example 238

Cell Proliferation Studies

Inhibition of OVCAR-3 Cells

Cells: OVCAR-3 cells, ATCC Passage 4, Mycoplasma free.

Medium: RPMI-1640 Medium (GIBCO Cat#22400121) supplemented with 10% fetal bovine serum (Hyclone Cat#SH30396.03).

Seeding: 2,000 cells/well (100 μL) into 96-well plates, incubated overnight at 37° C. in a humidified 5% CO_2 atmosphere.

Treatment: Test compounds were first diluted 333-fold in the medium. Fifty microliters (50 μL) of diluted compounds were added into each well (i.e., another 3-fold dilution). The final concentration of test compounds was 10 μM. The final concentrations of the positive control (Gemcitabine, also 50 μL added in each well) is shown in FIG. **42**. The cells were incubated for 72 hours after addition of the test compounds.

MTS: Added 20 μL of MTS solution (Promega Cat #G5430) into each well and incubated for 4 hours.

Calculation: % of inhibition+(AVE zero ctrl−AVE compound)/AVE zero ctrl*100.

Results are shown in Table 13:

TABLE 13

Compound ID	Test No.	OD value			Color control	Real OD			Avg.	Inhibition Rate %
4981	1	0.777	0.872	0.917	0.267	0.510	0.606	0.650	0.589	19.2
4985	2	0.895	0.937	0.902	0.280	0.615	0.657	0.622	0.631	13.3
4991	3	0.532	0.557	0.571	0.252	0.280	0.305	0.319	0.301	58.7
4999	4	0.794	0.882	0.793	0.254	0.540	0.628	0.538	0.569	22.0
CON	—	1.010	0.948	1.020	0.264	0.746	0.684	0.756	0.728	0.0
	1.2 μM	0.781	0.948	0.851	0.264	0.517	0.684	0.586	0.596	18.2
	3.7 μM	0.784	0.770	0.876	0.264	0.520	0.506	0.612	0.546	25.0
	11.1 μM	0.742	0.749	0.797	0.264	0.478	0.485	0.532	0.499	31.5
	33.3 μM	0.638	0.687	0.760	0.264	0.374	0.423	0.496	0.431	40.8
	100 μM	0.378	0.331	0.408	0.264	0.114	0.067	0.144	0.108	85.1
	300 μM	0.335	0.385	0.356	0.264	0.071	0.121	0.092	0.095	87.0

Example 239

Cell Proliferation Studies

Inhibition of LNCaP Cells

Cells: LNCaP, ATCC Passage unknown, Mycoplasma free.

Medium: RPMI-1640 Medium (GIBCO Cat#22400121) supplemented with 10% fetal bovine serum (Hyclone Cat#SH30396.03).

Seeding: 3,000 cells/well (100 μL) into 96-well plates, incubated overnight at 37° C. in a humidified 5% CO_2 atmosphere.

Treatment: Test compounds were first diluted 333-fold in the medium. Fifty microliters (50 μL) of diluted compounds were added into each well (i.e., another 3-fold dilution). The final concentration of test compounds was 10 μM. The final concentrations of the positive control (Gemcitabine, also 50 μL added in each well) is shown in FIG. **43**. The cells were incubated for 72 hours after addition of the test compounds.

MTS: Added 20 μL of MTS solution (Promega Cat #G5430) into each well and incubated for 4 hours.

Calculation: % of inhibition+(AVE zero ctrl−AVE compound)/AVE zero ctrl*100.

Results are shown in Table 14:

TABLE 14

Compound ID	Test No.	OD value			Color control	Real OD			Average	Inhibition Rate %
4981	1	1.532	1.471	1.686	0.264	1.267	1.207	1.422	1.299	4.1
4985	2	1.376	1.317	1.853	0.273	1.103	1.044	1.580	1.243	8.3
4991	3	1.328	1.361	1.414	0.267	1.061	1.094	1.147	1.100	18.8
4999	4	1.455	1.602	1.584	0.283	1.173	1.319	1.301	1.264	6.7
Con	—	1.714	1.505	1.647	0.267	1.446	1.237	1.37	1.355	0.0
	1.2 μM	1.403	1.394	1.480	0.267	1.135	1.126	1.213	1.158	14.5
	3.7 μM	0.730	0.814	0.847	0.267	0.463	0.547	0.579	0.530	60.9
	11.1 μM	0.379	0.410	0.413	0.267	0.112	0.142	0.145	0.133	90.2
	33.3 μM	0.363	0.375	0.353	0.267	0.096	0.107	0.086	0.097	92.9
	100 μM	0.377	0.406	0.396	0.267	0.109	0.139	0.128	0.126	90.7
	300 μM	0.401	0.413	0.391	0.267	0.134	0.145	0.123	0.134	90.1

Example 240

Cell Proliferation Studies

Inhibition of Jurkat Cells

Cells: Jurkat cells, ATCC Passage unknown, Mycoplasma free.

Medium: RPMI-1640 Medium (GIBCO Cat#22400121) supplemented with 10% fetal bovine serum(Hyclone Cat#SH30396.03).

Seeding: 5,000 cells/well (100 μL) into 96-well plates, incubated overnight at 37° C. in a humidified 5% CO_2 atmosphere.

Treatment: Test compounds were first diluted 333-fold in the medium. Fifty microliters (50 μL) of diluted compounds were added into each well (i.e., another 3-fold dilution). The final concentration of test compounds was 10 μM. The final concentrations of the positive control (Gemcitabine, also 50 μL added in each well) is shown in FIG. **44**. The cells were incubated for 72 hours after addition of the test compounds.

MTS: Added 20 μL of MTS solution (Promega Cat #G5430) into each well and incubated for 4 hours.

Calculation: % of inhibition+(AVE zero ctrl−AVE compound)/AVE zero ctrl*100.

Results are shown in Table 15:

TABLE 15

Compound ID	Test No.	OD value			Color control	Real OD			Average	Inhibition Rate %
4981	1	0.752	0.847	0.793	0.292	0.460	0.555	0.501	0.505	−2.2
4985	2	0.660	0.620	0.613	0.302	0.357	0.318	0.311	0.329	33.5
4991	3	0.557	0.480	0.469	0.288	0.269	0.192	0.181	0.214	56.8
4999	4	0.718	0.694	0.622	0.274	0.443	0.419	0.348	0.403	18.4
Con	—	0.830	0.659	0.827	0.278	0.552	0.382	0.548	0.494	0.0
	1.2 μM	0.659	0.674	0.725	0.278	0.381	0.396	0.447	0.408	17.4
	3.7 μM	0.457	0.465	0.447	0.278	0.179	0.187	0.169	0.179	63.9
	11.1 μM	0.355	0.354	0.352	0.278	0.077	0.076	0.0742	0.076	84.7
	33.3 μM	0.254	0.249	0.254	0.278	−0.024	−0.029	−0.0234	−0.026	105.2
	100 μM	0.254	0.247	0.252	0.278	−0.024	−0.031	−0.0258	−0.027	105.5
	300 μM	0.261	0.258	0.255	0.278	−0.017	−0.020	−0.0231	−0.020	104.1

Example 241

Cell Proliferation Studies

Inhibition of MDA-MB-468 Cells

Cells: MDA-MB-468 cells, ATCC Passage unknown, Mycoplasma free.

Medium: RPMI-1640 Medium (GIBCO Cat#22400121) supplemented with 10% fetal bovine serum (Hyclone Cat#SH30396.03).

Seeding: 2,000 cells/well (100 μL) into 96-well plates, incubated overnight at 37° C. in a humidified 5% CO_2 atmosphere.

Treatment: Test compounds were first diluted 333-fold in the medium. Fifty microliters (50 μL) of diluted compounds were added into each well (i.e., another 3-fold dilution). The final concentration of test compounds was 10 μM. The final concentrations of the positive control (Gemcitabine, also 50 μL added in each well) is shown in FIG. **45**. The cells were incubated for 72 hours after addition of the test compounds.

MTS: Added 20 μL of MTS solution (Promega Cat #G5430) into each well and incubated for 4 hours.

Calculation: % of inhibition+(AVE zero ctrl−AVE compound)/AVE zero ctrl*100.

Results are shown in Table 16:

TABLE 16

Compound ID	Test No.	OD value			Color control	Real OD			Average	Inhibition Rate %
4981	1	0.733	1.158	0.739	0.334	0.400	0.824	0.405	0.543	22.6
4985	2	0.845	1.107	0.893	0.280	0.565	0.828	0.613	0.669	4.7
4991	3	0.688	0.936	0.665	0.278	0.411	0.659	0.388	0.486	30.8
4999	4	0.800	1.145	0.849	0.271	0.529	0.874	0.578	0.660	5.9
CON	—	0.996	0.990	0.937	0.273	0.723	0.717	0.663	0.702	0.0
	1.2 μM	0.871	0.867	0.840	0.273	0.598	0.594	0.567	0.586	16.4
	3.7 μM	0.735	0.765	0.765	0.273	0.463	0.492	0.492	0.482	31.2
	11.1 μM	0.428	0.364	0.431	0.273	0.156	0.091	0.158	0.135	80.7
	33.3 μM	0.332	0.324	0.336	0.273	0.060	0.051	0.0629	0.058	91.7
	100 μM	0.331	0.318	0.405	0.273	0.058	0.045	0.132	0.078	88.8
	300 μM	0.323	0.294	0.309	0.273	0.050	0.022	0.0359	0.036	94.9

Example 242

Cell Proliferation Studies

Inhibition of HCT116 Cells

Cells: HCT116 cells, ATCC Passage unknown, Mycoplasma free.

Medium: DMEM Medium (GIBCO Cat#11995073) supplemented with 10% fetal bovine serum (Hyclone Cat#SH30396.03).

Seeding: 750 cells/well (100 μL) into 96-well plates, incubated overnight at 37° C. in a humidified 5% CO_2 atmosphere.

Treatment: Test compounds were first diluted 333-fold in the medium. Fifty microliters (50 μL) of diluted compounds were added into each well (i.e., another 3-fold dilution). The final concentration of test compounds was 10 μM. The final concentrations of the positive control (Gemcitabine, also 50 μL added in each well) is shown in FIG. **46**. The cells were incubated for 72 hours after addition of the test compounds.

MTS: Added 20 μL of MTS solution (Promega Cat #G5430) into each well and incubated for 4 hours.

Measurement: Absorbance at 490 nm using MD Spectramax Plus 384 spectrophotometer.

Calculation: % of inhibition+(AVE zero ctrl−AVE compound)/AVE zero ctrl*100.

Results are shown in Table 17:

TABLE 17

Compound ID	Test No.	OD value			Color control	Real OD			Average	Inhibition Rate %
4981	1	1.906	1.900	1.911	0.356	1.550	1.544	1.555	1.550	8.9
4985	2	1.922	2.285	1.880	0.380	1.542	1.905	1.501	1.649	3.1
4991	3	1.750	1.645	1.744	0.352	1.399	1.293	1.392	1.361	20.0
4999	4	1.864	1.979	1.997	0.357	1.506	1.621	1.640	1.589	6.6
CON	control	2.034	1.970	2.160	0.353	1.681	1.617	1.807	1.702	0.0
	1.2 μM	1.171	1.242	1.192	0.353	0.819	0.889	0.839	0.849	50.1
	3.7 μM	0.707	0.640	0.768	0.353	0.355	0.287	0.415	0.352	79.3
	11.1 μM	0.573	0.565	0.653	0.353	0.220	0.213	0.300	0.244	85.6
	33.3 μM	0.591	0.575	0.626	0.353	0.238	0.222	0.274	0.245	85.6
	100 μM	0.541	0.606	0.655	0.353	0.188	0.254	0.303	0.248	85.4
	300 μM	0.546	0.563	0.584	0.353	0.194	0.211	0.231	0.212	87.6

Example 243

Cell Proliferation Studies

Inhibition of A549 Cells

Cells: A549 cells, ATCC Passage unknown, Mycoplasma free.

Medium: DMEM Medium (GIBCO Cat#11995073) supplemented with 10% fetal bovine serum (Hyclone Cat#SH30396.03).

Seeding: 750 cells/well (100 μL) into 96-well plates, incubated overnight at 37° C. in a humidified 5% CO_2 atmosphere.

Treatment: Test compounds were first diluted 333-fold in the medium. Fifty microliters (50 μL) of diluted compounds were added into each well (i.e., another 3-fold dilution). The final concentration of test compounds was 10 μM. The final concentrations of the positive control (Gemcitabine, also 50 μL added in each well) is shown in FIG. **47**. The cells were incubated for 72 hours after addition of the test compounds.

MTS: Added 20 μL of MTS solution (Promega Cat #G5430) into each well and incubated for 4 hours.

Measurement: Absorbance at 490 nm using MD Spectramax Plus 384 spectrophotometer.

Calculation: % of inhibition+(AVE zero ctrl−AVE compound)/AVE zero ctrl*100.

Results are shown in Table 18:

TABLE 18

Compound ID	Test No.	OD value			Color control	Real OD			Average	Inhibition Rate %
4981	1	1.610	1.820	1.696	0.358	1.253	1.462	1.338	1.351	2.9
4985	2	1.756	1.753	1.799	0.401	1.356	1.352	1.398	1.368	1.7
4991	3	1.632	1.602	1.611	0.306	1.326	1.295	1.305	1.309	6.0
4999	4	1.797	1.738	1.789	0.387	1.410	1.351	1.402	1.388	0.3
CON	control	1.848	1.806	1.585	0.354	1.494	1.451	1.231	1.392	0.0
	1.2 μM	1.197	1.282	1.158	0.354	0.843	0.928	0.804	0.858	38.3
	3.7 μM	0.840	0.864	0.854	0.354	0.485	0.510	0.500	0.498	64.2
	11.1 μM	0.733	0.750	0.762	0.354	0.378	0.396	0.407	0.394	71.7
	33.3 μM	0.745	0.703	0.746	0.354	0.390	0.348	0.391	0.377	72.9
	100 μM	0.651	0.643	0.671	0.354	0.297	0.289	0.317	0.301	78.4
	300 μM	0.629	0.593	0.652	0.354	0.275	0.238	0.298	0.270	80.6

Example 244

Cell Proliferation Studies

Inhibition of DU145 Cells

Cells: DU145 cells, ATCC Passage unknown, Mycoplasma free.

Medium: DMEM Medium (GIBCO Cat#11995073) supplemented with 10% fetal bovine serum (Hyclone Cat#SH30396.03).

Seeding: 750 cells/well (100 μL) into 96-well plates, incubated overnight at 37° C. in a humidified 5% CO_2 atmosphere.

Treatment: Test compounds were first diluted 333-fold in the medium. Fifty microliters (50 μL) of diluted compounds were added into each well (i.e., another 3-fold dilution). The final concentration of test compounds was 10 μM. The final concentrations of the positive control (Gemcitabine, also 50 μL) added in each well) is shown in FIG. **48**. The cells were incubated for 72 hours after addition of the test compounds.

MTS: Added 20 μl_, of MTS solution (Promega Cat #G5430) into each well and incubated for 4 hours.

Measurement: Absorbance at 490 nm using MD Spectramax Plus 384 spectrophotometer.

Calculation: % of inhibition+(AVE zero ctrl−AVE compound)/AVE zero ctrl*100.

Results are shown in Table 19:

TABLE 19

Compound ID	Test No.	OD value			Color control	Real OD			Average	Inhibition Rate %
4981	1	1.360	1.205	1.427	0.259	1.100	0.946	1.168	1.071	8.4
4985	2	1.522	1.724	1.551	0.411	1.112	1.314	1.140	1.188	−1.6
4991	3	1.487	1.516	1.512	0.367	1.120	1.149	1.145	1.138	2.7
4999	4	1.592	1.591	1.538	0.290	1.302	1.302	1.248	1.284	−9.8
CON	control	1.470	1.566	1.469	0.332	1.138	1.234	1.137	1.170	0.0
	1.2 μM	0.858	0.947	0.930	0.332	0.526	0.615	0.598	0.580	50.4
	3.7 μM	0.424	0.448	0.428	0.332	0.093	0.116	0.097	0.102	91.3
	11.1 μM	0.418	0.412	0.447	0.332	0.087	0.081	0.115	0.094	91.9
	33.3 μM	0.404	0.425	0.457	0.332	0.072	0.093	0.125	0.097	91.7
	100 μM	0.453	0.426	0.355	0.332	0.121	0.094	0.023	0.079	93.2
	300 μM	0.410	0.395	0.400	0.332	0.079	0.063	0.068	0.070	94.0

Example 245

Cell Proliferation Studies

Inhibition of HCC1954 Cells

Cells: DU145 cells, ATCC Passage unknown, Mycoplasma free.

Medium: RPMI-1640 Medium (GIBCO Cat#22400121) supplemented with 10% fetal bovine serum (Hyclone Cat#SH30396.03).

Seeding: 2,000 cells/well (100 μL) into 96-well plates, incubated overnight at 37° C. in a humidified 5% CO_2 atmosphere.

Treatment: Test compounds were first diluted 333-fold in the medium. Fifty microliters (50 μL) of diluted compounds were added into each well (i.e., another 3-fold dilution). The final concentration of test compounds was 10 μM. The final concentrations of the positive control (Sorafenib, also 50 μL added in each well) is shown in FIG. **49**. The cells were incubated for 72 hours after addition of the test compounds.

MTS: Added 20 μL of MTS solution (Promega Cat #G5430) into each well and incubated for 4 hours.

Measurement: Absorbance at 490 nm using MD Spectramax Plus 384 spectrophotometer.

Calculation: % of inhibition+(AVE zero ctrl−AVE compound)/AVE zero ctrl*100.

Results are shown in Table 20:

TABLE 20

Compound ID	Test No.	OD value			Color control	Real OD			Average	Inhibition Rate %
4981	1	1.595	1.746	1.796	0.286	1.309	1.461	1.510	1.427	2.2
4985	2	1.767	1.793	2.086	0.237	1.530	1.556	1.848	1.645	−12.8
4991	3	1.702	1.771	1.804	0.239	1.462	1.531	1.565	1.519	−4.2
4999	4	1.617	1.823	1.816	0.227	1.389	1.596	1.589	1.525	−4.6
Con	control	1.470	1.861	1.772	0.243	1.227	1.618	1.529	1.458	0.0
	1.2 μM	1.750	1.557	1.710	0.243	1.507	1.314	1.467	1.429	2.0
	3.7 μM	1.694	1.560	1.554	0.243	1.451	1.317	1.311	1.360	6.8
	11.1 μM	1.479	1.601	1.482	0.243	1.236	1.358	1.238	1.278	12.4
	33.3 μM	0.296	0.265	0.275	0.243	0.053	0.022	0.032	0.036	97.5
	100 μM	0.324	0.309	0.313	0.243	0.081	0.066	0.070	0.072	95.0
	300 μM	0.526	0.522	0.539	0.243	0.283	0.279	0.296	0.286	80.4

Example 246

Cell Proliferation Studies

Inhibition of Caco-2 Cells

Cells: Caco-2 cells, ATCC Passage 109, Mycoplasma free.

Medium: DMEM Medium (GIBCO Cat#11995073) supplemented with 10% fetal bovine serum (Hyclone Cat#SH30396.03).

Seeding: 3,000 cells/well (100 μL) into 96-well plates, incubated overnight at 37° C. in a humidified 5% CO_2 atmosphere.

Treatment: Test compounds were first diluted 333-fold in the medium. Fifty microliters (50 μL) of diluted compounds were added into each well (i.e., another 3-fold dilution). The final concentration of test compounds was 10 μM. The final concentrations of the positive control (Sorafenib, also 50 μL added in each well) is shown in FIG. **50**. The cells were incubated for 72 hours after addition of the test compounds.

MTS: Added 20 μL of MTS solution (Promega Cat #G5430) into each well and incubated for 4 hours.

Measurement: Absorbance at 490 nm using MD Spectramax Plus 384 spectrophotometer.

Calculation: % of inhibition+(AVE zero ctrl−AVE compound)/AVE zero ctrl*100.

Results are shown in Table 21:

TABLE 21

Compound ID	Test No.	OD value			Color control	Real OD			Average	Inhibition Rate %
4981	1	1.392	1.571	1.473	0.391	1.001	1.180	1.082	1.088	3.8
4985	2	1.535	1.572	1.512	0.351	1.184	1.221	1.160	1.188	−5.1
4991	3	1.319	1.287	1.344	0.367	0.952	0.920	0.977	0.949	16.0
4999	4	1.393	1.485	1.432	0.342	1.051	1.143	1.090	1.094	3.2
Con	control	1.415	1.516	1.499	0.346	1.068	1.169	1.153	1.130	0.0
	1.2 μM	1.528	1.497	1.430	0.346	1.182	1.151	1.083	1.139	−0.7
	3.7 μM	1.471	1.408	1.436	0.346	1.124	1.062	1.089	1.092	3.4
	11.1 μM	1.090	1.098	1.139	0.346	0.743	0.752	0.792	0.763	32.5
	33.3 μM	0.393	0.383	0.366	0.346	0.047	0.037	0.020	0.034	96.9
	100 μM	0.418	0.396	0.392	0.346	0.072	0.050	0.045	0.056	95.1
	300 μM	0.579	0.600	0.638	0.346	0.233	0.253	0.292	0.259	77.1

Example 247

IC_{50} determination of compound 4991 against three cancer cell lines

Additional cell inhibition studies were performed by Crown Biosciences. The materials are described in Table 22.

TABLE 22

Human cancer	Cell line	Medium	Positive drug	Incubation time
Ovary cancer	OVCAR-3	RPMI 1640 + 10% FBS	Cisplatin	72 h
	OVCAR-8	RPMI 1640 + 10% FBS		72 h
	SK-OV-3	McCoy's 5a + 10% FBS		72 h

The dose response curves of compound 4991 compared to cisplatin, as well as the calculated IC_{50} values, are shown in FIGS. **51-53**.

Example 248

In vitro ADME assays of PAMPA and human and rat hepatic microsomal stability.

The generic gradient HPLC and MS method summarized in Table 22 was used for the analysis of compounds 4981, 4985, 4991 and 4999.

TABLE 23

HPLC conditions.			
Instrument	Applied Biosystems API 4000 mass spectrometer		
Ionization Mode	Electrospray, positive ions		
MRM	4981: 382.2 → 178.1 4985: 369.1 → 178.1 4991: 370.1 → 178.1 4999: 368.2 → 178.1		
Column	ACE 2 C18, 2.1 × 50 mm, 3 μm		
Eluent A	2 mM ammonium acetate, 0.1% formic acid in 95:5 water:methanol		
Eluent B	2 mM ammonium acetate, 0.1% formic acid in 95:5 methanol:water		
	Time (min)	% A	% B
Pump Gradient Program	0	75	25
	0.5	75	25
	1.00	0	100
	2.00	0	100
	2.10	75	25
	2.50	75	25

TABLE 23-continued

HPLC conditions.	
Flow (mL/min)	0.5
Column Temperature	Ambient
Injection Volume	3-30
Sample Temperature	Ambient
Run Time (min)	2.5

Parallel artificial membrane permeability assays (PAMPA) were performed with the compounds 4981, 4985, 4991 and 4999. The target concentration in the assay was 10 μM, prepared by diluting (1000-fold) the 10 mM stock solutions in DMSO into PBS, pH 7.4. The final DMSO concentration was 0.1%. The 10 μM solutions were added, 300 μL, to wells in the donor plate. The receiver plate, which contained 200 μL of PBS, pH 7.4 per well, was placed in the donor plate and the assembly was incubated for 5 hours at ambient temperature. At the end of the incubation period the plates were separated and the compound concentrations in each solution were determined by LC/MS/MS. The assay was performed in triplicate. Dexamethasone and verapamil were used as reference compounds. The permeability, P_e, and mass retention, R, of each compound were calculated using the following equations, and the results are summarized in Table 17. The results for dexamethsone and verapamil were consistent with historical data.

$$P_e = \frac{-\ln[1 - C_{A(t)}/C_0] \times 10^7}{A \times (1/V_D + 1/V_A) \times t}$$

$$R = 1 - \frac{C_{D(t)}V_D + C_{A(t)}V_A}{C_0 V_D}$$

Where:

C_0 is the initial concentration in the donor well (μM)

$C_{D(t)}$ is the concentration in the donor well after incubation (μM)

$C_{A(t)}$ is the concentration in the acceptor well after incubation (μM)

V_D is the volume in the donor well (0.3 mL)

V_A is the volume in the acceptor well (0.2 mL)

C_E is $(C_{D(t)}V_D+C_{A(t)}V_A)/(V_D+V_A)$

A is the filter area (0.3 cm2)

t is the incubation time (18,000 s).

TABLE 24

PAMPA Assay data summary.

Compound	Permeability P_e (nm/s)	Mass Retention R (%)
4981	6.0	0
4985	125	20
4991	99	0
4999	48	35
Verapamil	75	20
Dexamethasone	9.0	9

Hepatic microsomal assays were performed with 4981, 4985, 4991 and 4999 in human and rat (Sprague-Dawley). Protein concentrations of 0.4 (human) and 0.2 mg/mL (rat) with an NADPH regenerating cofactor system (2.6 mM NADP+, 6.6 mM glucose-6-phosphate, 0.8 U/mL glucose-6-phosphate dehydrogenase, and 6.6 mM magnesium chloride) were used. A 100 μM 20% DMSO/80% acetonitrile working stock of each of the compounds was diluted 100 fold resulting in 1 μM compound/1% final organic reaction concentrations. Time points were removed at 0 and 60 minutes. At each time point, 100 μL of the incubation suspension was added to 200 μL of acetonitrile containing internal standard (tolbutamide), followed by centrifugation at 3,220 rcf for 10 minutes. Two hundred (200)μL of the resulting supernatants were removed, dried under nitrogen and reconstituted in 100 μL of 2 mM ammonium acetate, 0.1% formic acid in 50% methanol prior to analysis by LC/MS/MS. Testosterone and dexamethasone were used as reference compounds. Table 25 summarizes the results. The results for testosterone and dexamethasone were consistent with historical data.

TABLE 25

Hepatic microsomal stability summary

	% remaining after incubation	
Compound	Rat Microsomes	Human Microsomes
4981	14	63
4985	0.4	46
4991	0.6	55
4999	0.4	3.6
Testosterone	0.6	42
Dexamethasone	91	85

Materials used are summarized in Table 26.

TABLE 26

Materials.

Material	Supplier	Part No.	Lot No.
Testosterone	Sigma	T1500	087K1440
Dexamethasone	Sigma	D1756	096K1805
Verapamil	Aldrich	381195	12731MA
Tolbutamide	Sigma	T0891	076K1277
PBS	Sigma	P3813	096K8204
Ammonium acetate	J.T. Baker	0599-08	E49H15
Formic acid	Acros Organics	147930250	AO266198
Acetonitrile	EMD	AX0145-1	49099
DMSO	Alfa Aeser	32434	D04R008
Isopropanol	J.T. Baker	9827-03	C38H23
Methanol	EMD	MX0486-1	49178
0.5M Potassium Phosphate pH 7.4	BD Gentest	451201	06123
PAMPA plate	BD Gentest	353015	431256
Human microsomes	BD Gentest	452161	18888

TABLE 26-continued

Materials.

Material	Supplier	Part No.	Lot No.
Rat microsomes	BD Gentest	452501	21027
NADPH Regeneration System Solution A	BD Gentest	451220	51893
NADPH Regeneration System Solution B	BD Gentest	451220	47758
water	House DI (Barnstead Nanopure)		

LC/MS Equipment:
Chromatograph: Shimadzu LC-20 AD
Autosampler: CTC HTS PAL
MS: API 4000
Software System Analyst Software, Version 1.4.2.

Example 249

Selected Cell Proliferation Inhibition Data
Cell Lines:

Human cancer	Cell line	Medium	Positive drug	Incubation time
Multiple Myeloma	MV4-11	IMDM	Cisplatin	72 hours
	RPMI-8226	RPMI-1640		
	NCI-H929	RPMI-1640 + 0.05 mM 2-mercaptoethanol		

All cells were cultured in media supplemented with 10% FBS except for which are marked specially, in the temperature of 37° C., 5% CO_2 and 95% humidity. All culture media were purchased from GIBCO (USA, IMDM Cat. 12200-036; RPMI Medium 1640 Cat. 31800-022; 2-mercaptoethanol Cat. 21985-023).

Reagents:

CellTiter 96® AQueous MTS reagent powder (Cat. No.: G1112, Promega. Store MTS Reagent Powder desiccated at 4° C. protected from light.)

Phenazine methosulfate (PMS) (Product No.: P9625, SIGMA. Store PMS Powder desiccated at 4° C. protected from light.)

Preparation of PMS Solution:

0.92 mg/mL PMS in DPBS Filter-sterilize through a 0.2 m filter into a sterile, lig0ht-protected container. Store at −20° C.

Preparation of MTS Solution:

The following protocol is recommended for the preparation of 21 mL of MTS solution (sufficient for ten 96-well plates).

a. Select a light-protected container or wrap a container with foil.
b. Add 21 mL of DPBS to the container.
c. Weigh out 42 mg of MTS Reagent Powder and add to DPBS.
d. Mix at moderate speed on a magnetic stir plate for 15 minutes or until the MTS is completely dissolved.
e. Measure the pH of the MTS solution. The optimum pH is between pH 6.0 to 6.5. If the solution is above pH 6.5, adjust to pH 6.5 with 1N HC1.
f. Filter-sterilize the MTS solution through a 0.2 μm filter into a sterile, light protected container.
g. Store the MTS solution at −20° C., protected from light.

Preparation of the Mixture of MTS/PMS:

a. In order to prepare reagents sufficient for one 96-well plate containing cells cultured in a 100 μL volume, thaw the

MTS solution and the PMS solution. It should take approximately 90 minutes at room temperature or 10 minutes in a 37° C. water bath to completely thaw the 20 mL size of MTS solution. (Note: For convenience, the first time the product is thawed, the entire contents of the 1 mL tube of PMS solution can be transferred to the 20 mL bottle of MTS solution. This mixture should be stored at −20° C. between uses. If storing PMS and MTS solutions at 4° C., do not combine these solutions until immediately before addition to the assay plate.)

b. Remove 2.0 mL of MTS solution from the amber reagent bottle using aseptic technique and transfer to a test tube.

c. Add 100 μL of PMS solution to the 2.0 mL of MTS solution immediately before addition to the culture plate containing cells.

d. Gently swirl the tube to ensure complete mixing of the combined MTS/PMS solution.

Equipment:

SpectraMAX plus microplate spectrophotometer Model 3011, Molecular Devices Corp. (California, USA); CO_2 water jacketed incubator, Therma (USA). Reverse microscope, Chongguang XDS-1B, Chongqing Guangdian Corp. (Chongqing, P.R. China).

Cytotoxicity and IC_{50} Determination:

1. The cells were harvested respectively during the logarithmic growth period and counted with hemocytometer. The cell viability was over 98% by trypan blue exclusion.
2. Cell concentrations were adjusted to 2.22×10^5 or 1.11×10^5 or 5.56×10^4 cells/mL with respective medium.
3. 90 μL cell suspensions were added to 96-well plates (triplicates for each cell concentration), the final cell densities were 2×10^4 or 1×10^4 or 5×10^3 cells/well. The density of 5×10^3 cells/well was used for the first test. The appropriate cell density was determined and adjusted according to the results of the first test.
4. The next day, test article or positive drugs were dissolved with DMSO as stock solution at the concentration of 20 mM.
5. 10 μL drug solution was dispensed in each well (triplicate for each drug concentration).
6. Plates were cultured for another 72 hours, then measured by means of MTS assay.
7. MTS/PMS solution was prepared immediately prior to use. 20 μL of the mixture was introduced into each well of the 96-well assay plate containing 100 μL culture medium. (The final reaction volume was 120 μL).
8. Plate was incubated for 1-4 hours at 37° C. in a humidified 5% CO_2 atmosphere.
9. Absorbance at 490 nm was recorded using SpectraMAX Plus microplate spectrophotometer.

Data Analysis:

The software of GraphPad Prism version 5 was used to calculate IC_{50}. The graphical curves were fitted using a non-linear regression model with a sigmoidal dose.

Results

Results are shown in Tables 27 and 28.

TABLE 27

	IC_{50} values (μM)		
Example	MV4-11	RPMI 8226	NCI-H929
155	12.49	NC	3.964
120	4.054	1.538	2.806
180	10.95	9.135	10.94
9	6.782	16.14	11.54
181	1.199	3.412	4.415

TABLE 27-continued

	IC_{50} values (μM)		
Example	MV4-11	RPMI 8226	NCI-H929
182	2.025	11.87	7.076
183	1/829	9.604	4.603
140	5.514	11.19	8.843
189	4.712	8.324	3.045
191	2.397	6.862	3.264

TABLE 28

	Percent inhibition at 30 μM of Compound		
Example	MV4-11	RPMI 8226	NCI-H929
155	97.60	53.87	73.72
120	95.09	76.43	89.78
180	90.71	79.74	100
9	91.08	71.25	91.44
181	96.63	82.15	93.5
182	91.09	90.21	96.52
183	94.36	82.34	98.62
140	94.29	65.26	96.73
189	97.91	99.87	98.51
191	87.43	93.08	93.96

Example 250

TABLE 29

	Percent Activity of Enzyme When Treated with 300 nM of Compound (ATP present at Km of enzyme)					
Example	CK1γ2(h)	CK1(y)	CK2(h)	Pim-1(h)	Pim-2(h)	Pim-3(h)
86	26		102	83	51	105
87	80		38	40	33	56
88	91		102	52	54	102
89	100		82	99	116	110
90	81		38	22	22	62
91	79		57	36	32	102
92	103	99	33	56	47	14
93	108	88	68	54	48	30
94	19	99	98	97	101	90
96	87	90	65	73	44	57
97	83	101	70	49	22	69
98	67	89	59	40	27	39
99	85	96	79	39	6	43
99	81	97	84	47	17	43
100	108	93	45	71	64	48
101	104	97	71	42	46	20
102	101	101	84	94	91	53
103	90	97	73	114	138	99
104	89	99	82	75	72	42
105	94	96	84	101	92	81
106	67	91	47	46	22	44
107	95	97	88	72	56	47
108	79	100	90	49	18	57
109	82	82	59	68	49	57
110	58	94	62	54	31	48
111	102	104	96	71	60	51
112	98	95	82	92	88	81
113	82	87	64	64	46	40
114	77	88	56	62	36	42
115	55	94	67	50	28	55
116	83	96	61	59	45	57
117	71	91	67	37	16	53
118	98	97	68	45	56	46
119	79	100	33	25	6	48
120	72	87	43	36	43	69
121	81	115	55	74	37	82
122	64	96	71	43	50	68

TABLE 29-continued

Example	CK1γ2(h)	CK1(y)	CK2(h)	Pim-1(h)	Pim-2(h)	Pim-3(h)
123	71	99	106	92	94	109
124	92	110	91	89	62	101
125	78	97	45	49	45	69
126	74	89	86	87	81	105
127	94	104	95	77	82	86
128	52	97	86	75	84	99
129	85	87	76	99	87	100
130	96	92	64	94	85	96
131	100	102	56	72	50	71
132	80	94	34	79	64	65
133	82	86	57	98	66	101
134	31	77	57	102	88	118
135	82	99	69	59	48	82
136	36	101	71	80	49	72
137	97	112	106	100	97	97
138	81	112	74	66	46	80
139	87	55	123	42	23	88
140	52	79	26	45	53	48
142	96		103	85	84	87
143	78	79	15	14	3	3
144	103	81	5	25	10	3
145	100	106	105	104	104	85
146	93	93	87	103	82	74
147	93	76	23	33	25	8
148	98	88	42	70	40	25
149	107	108	53	74	40	49
150	97	97	77	49	29	23
151	95	78	42	38	19	23
152	98	98	64	85	58	39
153	100	88	69	89	85	54
154	98	106	77	45	30	16
155	98	88	74	7	12	5
156	83	99	54	83	68	87
157	63	89	80	53	30	13
158	53	96	96	90	94	115
159	93	95	62	49	22	27
161	101	97	71	31	46	30
162	97	101	73	86	67	76
163	94	105	108	99	90	100
164	112	98	109	97	108	90
165	102	106	97	91	88	90
166	103	104	109	18	61	61
167	108	127	91	14	44	2
168	100		99	48	47	82
171	101	103	79	96	95	89
172	105	96	81	33	36	21
173	101	104	87	90	99	106
174	81	84	75	18	21	8
175	46	82	102	51	57	61
176	86	87	67	28	34	15
177	87	86	76	22	26	12
178	91	101	75	105	89	96
179	110	105	105	96	104	95
180	66	84	80	8	15	11
181	63	72	73	17	16	8
182	56	86	61	9	10	4
183	91	60	73	5	7	3
184	84	95	81	19	28	9
185	87	91	71	23	26	6
186	86	67	72	18	22	12
187	88	95	77	40	53	16
188	85	81	71	36	41	16
189	33	38	49	1	6	3
190	60	64	73	3	16	2
191	65	64	63	4	14	4
192	52	95	80	45	37	46
193	90	89	71	26	34	12
194	72	66	75	17	24	6
195	84	92	81	36	25	11
196	99	99	93	50	55	51
197	102	106	94	43	58	54
198	104	106	98	60	44	36
199	91	98	107	99	90	99
200	92	101	101	95	92	100

TABLE 29-continued

Example	CK1γ2(h)	CK1(y)	CK2(h)	Pim-1(h)	Pim-2(h)	Pim-3(h)
201	103	110	104	93	92	106
202	84	97	85	84	72	87
203	95	103	84	25	58	51
204	91	86	74	19	40	25
205	88	72	81	24	47	17
206	103	87	21	48	26	24
207	103	77	94	18	67	20
208	99	104	39	36	17	21
209	91	106	54	42	41	42
211	54	93	106	71	24	61
212	28	96	90	75	46	53
214	41	79	77	25	13	16
215	51	86	97	34	22	41
216	39	92	60	40	10	76
217	109		116	101	91	105
218	82		80	96	91	100
219	55	100	58	57	41	50
220	98	114	102	98	91	115
221	97	90	85	92	78	78
222	37	78	67	69	25	78
223	28	100	89	56	23	79
224	53	64	71	16	15	9
225	66	91	67	61	47	55

Example 251

TABLE 30

IC_{50} of Compound (nM) (ATP present at Km of enzyme)

Example	CK1γ2(h)	CK1(y)	CK2(h)	Pim-1(h)	Pim-2(h)	Pim-3(h)
86	86					
87			261	295	80	263
90			291	97	89	419
91			222	255	127	1000
92			186	628	228	31
94	38					
98			422	204	136	169
99				137	18	199
106			361	166	127	298
117				164	50	436
119			176	186	16	267
120	676	>1000	214	170	225	271
143			66	20	5	3
144			23	78	18	9
147			134	258	90	31
151			415	246	98	171
155				19	14	9
159				>1000	104	231
172				157	142	46
174				58	75	16
176			669	487	108	18
177			705	96	87	22
180				13	15	15
181				79	44	34
189	164	334	364	4	9	4
191				6	23	5
204				99	217	109
205				54	199	38
208			129	288	43	65
214				95	35	60
219			476	475	146	249

INCORPORATION BY REFERENCE

All of the U.S. patents and U.S. published patent applications cited herein are hereby incorporated by reference.

EQUIVALENTS

While several embodiments of the present invention have been described and illustrated herein, those of ordinary skill in the art will readily envision a variety of other means and/or structures for performing the functions and/or obtaining the results and/or one or more of the advantages described herein, and each of such variations and/or modifications is deemed to be within the scope of the present invention. More generally, those skilled in the art will readily appreciate that all parameters, dimensions, materials, and configurations described herein are meant to be exemplary and that the actual parameters, dimensions, materials, and/or configurations will depend upon the specific application or applications for which the teachings of the present invention is/are used. Those skilled in the art will recognize, or be able to ascertain using no more than routine experimentation, many equivalents to the specific embodiments of the invention described herein. It is, therefore, to be understood that the foregoing embodiments are presented by way of example only and that, within the scope of the appended claims and equivalents thereto, the invention may be practiced otherwise than as specifically described and claimed. The present invention is directed to each individual feature, system, article, material, kit, and/or method described herein. In addition, any combination of two or more such features, systems, articles, materials, kits, and/or methods, if such features, systems, articles, materials, kits, and/or methods are not mutually inconsistent, is included within the scope of the present invention.

SEQUENCE LISTING

<160> NUMBER OF SEQ ID NOS: 1

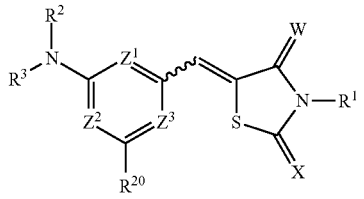
<210> SEQ ID NO 1
<211> LENGTH: 14
<212> TYPE: PRT
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic peptide

<400> SEQUENCE: 1

Lys Arg Arg Arg Ala Leu Ser Val Ala Ser Leu Pro Gly Leu
1 5 10

We claim:

1. A method of treating cancer, comprising administering to a mammal in need thereof a therapeutically effective amount of a compound of formula 1:



or a pharmaceutically acceptable salt thereof, wherein independently for each occurrence:

W and X are independently oxygen or sulfur;

Z^1, Z^2 and Z^3 are independently C—R^{20} or N, provided that at least one of Z^1 and Z^2 is N;

R^1 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl, heterocyclyl, aralkyl, heteroaralkyl, heterocyclylalkyl, —COR^6, —$C(O)OR^6$, —$SO_2(R^6)$, —$C(O)N(R^6)(R^7)$, —$SO_2N(R^6)(R^7)$, and —$[C(R^4)_2]_p$—R^5;

R^2 and R^3 are each independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl, heterocyclyl, aralkyl, heteroaralkyl, heterocyclylalkyl, —$[C(R^4)_2]_p$—R^5, —COR^6, —$C(O)OR^6$, —$SO_2(R^6)$, —$C(O)N(R^6)(R^7)$, —$SO_2N(R_6)(R^7)$, —$P(O)(OR^6)(OR^7)$; or R^2 and

R^3 are joined together to form an optionally substituted heterocyclic ring;

R^4 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, heterocyclylalkyl, aralkyl, heteroaryl, heteroaralkyl, halo, hydroxy, alkoxy, hydroxyalkyl, and alkoxyalkyl;

R^5 is selected from the group consisting of aryl, heteroaryl, heterocyclyl, —$N(R^8)(R^9)$, —$N(R^8)COR^9$, —$N(R^8)C(O)OR^9$, —$N(R^8)SO_2(R^9)$, —$CON(R^8)(R^9)$, —$OC(O)N(R^8)$—(R^9), —$SO_2N(R^8)(R^9)$, —$OC(O)OR^8$, —$COOR^9$, —$C(O)N(OH)(R^8)$, —$OS(O)_2OR^8$, —$S(O)_2OR^8$, —$S(O)_2R^8$, —OR^8, —COR^8, —$OP(O)(OR^8)(OR^8)$, —$P(O)(OR^8)(OR^8)$ and —$N(R^8)P(O)(OR^9)(OR^9)$;

R^6 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl, heterocyclyl, aralkyl, heteroaralkyl, and heterocyclylalkyl;

R^7 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl, heterocyclyl, aralkyl, heteroaralkyl, and heterocyclylalkyl; or R^6 and R^7 are joined together to form a heterocyclic ring;

R^8 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl, heterocyclyl, aralkyl, heteroaralkyl, and heterocyclylalkyl;

R^9 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl, heterocyclyl, aralkyl, heteroaralkyl, and heterocyclylalkyl; or R^8 and R^9 are joined together to form a heterocyclic ring;

R^{20} is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl, heterocyclyl, aralkyl, heteroaralkyl, heterocyclylalkyl, halo, haloalkyl, trifluoromethyl, fluoroalkyl, perfluoroalkyl, thio, cyano, hydroxy, methoxy, alkoxy, phenoxy, ary-

loxy, heteroaryloxy, carboxyl, alkoxycarbonyl, acyl, nitro, amino, alkylamino, arylamino, heteroarylamino, amido, acylamino, sulfate, sulfonate, sulfonyl, sulfoxido, sulfonamido, sulfamoyl, $—[C(R^4)_2]_p—R^5$, $NR^{14}R^{15}$, OR^{16}, $O—[C(R^4)_2]_p—R^5$, $NR^{14}—[C(R^4)_2]_p—R^5$ and SR^{16};

R^{14} and R^{15} are each independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl, heterocyclyl, aralkyl, heteroaralkyl, heterocyclylalkyl, $—[C(R^4)_2]_p—R^5$, $—COR^6$, $—C(O)OR^6$, $—SO_2(R^6)$, $—C(O)N(R^6)(R^7)$, $—SO_2N(R^6)(R^7)$, and $—P(O)(OR^6)(OR^7)$; or R^{14} and R^{15} are joined together to form an optionally substituted heterocyclic ring;

R^{16} is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl, heterocyclyl, aralkyl, heteroaralkyl, heterocyclylalkyl, $—[C(R^4)_2]_p—R^5$, $—COR^6$, and $—C(O)N(R^6)(R^7)$; and

p is 1, 2, 3, 4, 5, or 6;

wherein any one of the aforementioned alkyl, alkenyl, alkynyl, aryl, heteroaryl, heterocyclyl, aralkyl, heteroaralkyl, and heterocyclylalkyl may be optionally substituted; and

wherein the cancer is selected from the group consisting of:

adrenocortical carcinoma; anal cancer; basal cell carcinoma; bladder cancer; breast cancer; bronchial adenomas/carcinoids; cervical cancer; colon cancer; colorectal cancer; endometrial cancer; esophageal cancer; extrahepatic bile duct cancer; gallbladder cancer; gastric (stomach) cancer; gastrointestinal carcinoid tumor; gestational trophoblastic tumor; head and neck cancer, hepatocellular (liver) cancer; hypopharyngeal cancer; kidney (renal cell) cancer; laryngeal cancer; lip and oral cavity cancer; metastatic squamous neck cancer with occult primary; multiple endocrine neoplasia syndrome; nasal cavity and paranasal sinus cancer; nasopharyngeal cancer; Non-Small Cell Lung cancer; oral cancer; oropharyngeal cancer; pancreatic cancer; parathyroid cancer; penile cancer; pituitary tumor; prostate cancer; rectal cancer; salivary gland cancer; skin carcinoma, Merkel Cell; small cell lung cancer; small intestine cancer; squamous cell carcinoma; thymoma; thymoma and thymic carcinoma; thyroid cancer; transitional cell cancer of the renal pelvis and ureter; urethral cancer; uterine cancer, endometrial; vaginal cancer; vulvar cancer; Wilms' Tumor;

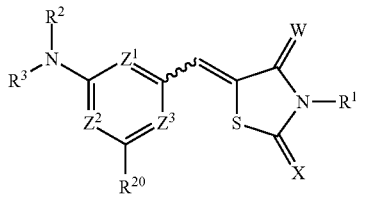
acute lymphoblastic leukemia; acute myeloid leukemia; AIDS-related lymphoma; Burkitt's lymphoma; chronic lymphocytic leukemia; chronic myelogenous leukemia; chronic myeloproliferative disorders; cutaneous T-cell lymphoma; hairy cell leukemia; hematologic (blood) cancer; Hodgkin's lymphoma; multiple myeloma/plasma cell neoplasm' mycosis fungoides; myelodysplastic syndromes; myelodysplastic/myeloproliferative diseases; multiple myeloma; Non-Hodgkin's lymphoma; primary central nervous system lymphoma; Sezary Syndrome; Waldenstrom's Macroglobulinemia;

Ewing's sarcoma; Kaposi's Sarcoma; osteosarcoma/malignant fibrous histiocytoma of bone; soft tissue sarcoma; uterine sarcoma;

extracranial germ cell tumor; extragonadal germ cell tumor; ovarian cancer; ovarian epithelial cancer; ovarian germ cell tumor; and testicular cancer.

2. A method of increasing apoptosis in cancerous cells, comprising administering to a mammal in need thereof a therapeutically effective amount of a compound of formula 1:

1



or a pharmaceutically acceptable salt thereof, wherein independently for each occurrence:

W and X are independently oxygen or sulfur;

Z^1, Z^2 and Z^3 are independently $C—R^{20}$ or N, provided that at least one of Z^1 and Z^2 is N;

R^1 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl, heterocyclyl, aralkyl, heteroaralkyl, heterocyclylalkyl, $—COR^6$, $—C(O)OR^6$, $—SO_2(R^6)$, $—C(O)N(R^6)(R^7)$, $—SO_2N(R^6)(R^7)$, and $—[(R^4)_2]_p—R^5$;

R^2 and R^3 are each independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl, heterocyclyl, aralkyl, heteroaralkyl, heterocyclylalkyl, $—[C(R^4)_2]_p—R^5$, $—COR^6$, $—C(O)OR^6$, $—SO_2(R^6)$, $—C(O)N(R^6)(R^7)$, $—SO_2N(^6)(R^7)$, $—P(O)(OR^6)(OR^7)$; or R^2 and

R^3 are joined together to form an optionally substituted heterocyclic ring;

R^4 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, heterocyclylalkyl, aralkyl, heteroaryl, heteroaralkyl, halo, hydroxy, alkoxy, hydroxyalkyl, and alkoxyalkyl;

R^5 is selected from the group consisting of aryl, heteroaryl, heterocyclyl, $—N(R^8)(R^9)$, $—N(R^8)COR^9$, $—N(R^8)C(O)OR^9$, $—N(R^8)SO_2(R^9)$, $—CON(R^8)(R^9)$, $—OC(O)N(R^8)—(R^9)$, $—SO_2N(R^8)(R^9)$, $—OC(O)OR^8$, $—COOR^9$, $—C(O)N(OH)(R^8)$, $—OS(O)_2OR^8$, $—S(O)_2OR^8$, $—S(O)_2R^8$, $—OR^8$, $—COR^8$, $—OP(O)(OR^8)(OR^8)$, $—P(O)(O^8)(OR^8)$ and $—N(R^8)P(O)(OR^9)(OR^9)$;

R^6 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl, heterocyclyl, aralkyl, heteroaralkyl, and heterocyclylalkyl;

R^7 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl, heterocyclyl, aralkyl, heteroaralkyl, and heterocyclylalkyl; or R^6 and R^7 are joined together to form a heterocyclic ring;

R^8 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl, heterocyclyl, aralkyl, heteroaralkyl, and heterocyclylalkyl;

R^9 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl, heterocyclyl, aralkyl, heteroaralkyl, and heterocyclylalkyl; or R^8 and R^9 are joined together to form a heterocyclic ring;

R^{20} is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl, heterocyclyl, aralkyl, heteroaralkyl, heterocyclylalkyl, halo, haloalkyl, trifluoromethyl, fluoroalkyl, perfluoroalkyl, thio, cyano, hydroxy, methoxy, alkoxy, phenoxy, aryloxy, heteroaryloxy, carboxyl, alkoxycarbonyl, acyl, nitro, amino, alkylamino, arylamino, heteroarylamino, amido, acylamino, sulfate, sulfonate, sulfonyl, sul-

foxido, sulfonamido, sulfamoyl, —$[C(R^4)_2]_p$—R^5, $NR^{14}R^{15}$, OR^{16}, O—$[C(R^4)_2]_p$—R^5, NR^{14}—$[C(R^4)_2]_p$—R^5 and SR^{16};

R^{14} and R^{15} are each independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl, heterocyclyl, aralkyl, heteroaralkyl, heterocyclylalkyl, —$[C(R^4)_2]_p$—R^5, —COR^6, —$C(O)OR^6$, —$SO_2(R^6)$, —$C(O)N(R^6)(R^7)$, —$SO_2N(R^6)(R^7)$, and —$P(O)(OR^6)(OR^7)$; or R^{14} and R^{15} are joined together to form an optionally substituted heterocyclic ring;

R^{16} is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl, heterocyclyl, aralkyl, heteroaralkyl, heterocyclylalkyl, —$[C(R^4)_2]_p$—R^5, —COR^6, and —$C(O)N(R^6)(R^7)$; and

p is 1, 2, 3, 4, 5, or 6;

wherein any one of the aforementioned alkyl, alkenyl, alkynyl, aryl, heteroaryl, heterocyclyl, aralkyl, heteroaralkyl, and heterocyclylalkyl may be optionally substituted; and

wherein the cancerous cells are cells of a cancer is selected from the group consisting of:

adrenocortical carcinoma; anal cancer; basal cell carcinoma; bladder cancer; breast cancer; bronchial adenomas/carcinoids; cervical cancer; colon cancer; colorectal cancer; endometrial cancer; esophageal cancer; extrahepatic bile duct cancer; gallbladder cancer; gastric (stomach) cancer; gastrointestinal carcinoid tumor; gestational trophoblastic tumor; head and neck cancer, hepatocellular (liver) cancer; hypopharyngeal cancer; kidney (renal cell) cancer; laryngeal cancer; lip and oral cavity cancer; metastatic squamous neck cancer with occult primary; multiple endocrine neoplasia syndrome; nasal cavity and paranasal sinus cancer; nasopharyngeal cancer; Non-Small Cell Lung cancer; oral cancer; oropharyngeal cancer; pancreatic cancer; parathyroid cancer; penile cancer; pituitary tumor; prostate cancer; rectal cancer; salivary gland cancer; skin carcinoma, Merkel Cell; small cell lung cancer; small intestine cancer; squamous cell carcinoma; thymoma; thymoma and thymic carcinoma; thyroid cancer; transitional cell cancer of the renal pelvis and ureter; urethral cancer; uterine cancer, endometrial; vaginal cancer; vulvar cancer; Wilms' Tumor;

acute lymphoblastic leukemia; acute myeloid leukemia; AIDS-related lymphoma; Burkitt's lymphoma; chronic lymphocytic leukemia; chronic myelogenous leukemia; chronic myeloproliferative disorders; cutaneous T-cell lymphoma; hairy cell leukemia; hematologic (blood) cancer; Hodgkin's lymphoma; multiple myeloma/plasma cell neoplasm' mycosis fungoides; myelodysplastic syndromes; myelodysplastic/myeloproliferative diseases; multiple myeloma; Non-Hodgkin's lymphoma; primary central nervous system lymphoma; Sezary Syndrome; Waldenstrom's Macroglobulinemia;

Ewing's sarcoma; Kaposi's Sarcoma; osteosarcoma/malignant fibrous histiocytoma of bone; soft tissue sarcoma; uterine sarcoma;

extracranial germ cell tumor; extragonadal germ cell tumor; ovarian cancer; ovarian epithelial cancer; ovarian germ cell tumor; and testicular cancer.

3. The method of claim **1**, wherein the cancer is selected from the group consisting of acute lymphoblastic leukemia; acute myeloid leukemia; AIDS-related lymphoma; breast cancer; Burkitt's lymphoma; chronic lymphocytic leukemia; chronic myelogenous leukemia; chronic myeloproliferative disorders; colon cancer; colorectal cancer; cutaneous T-cell lymphoma; Ewing's sarcoma; gastric (stomach) cancer; gastrointestinal carcinoid tumor; hairy cell leukemia; head and neck cancer; hematologic (blood) cancer, hepatocellular (liver) cancer; Hodgkin's lymphoma; lip and oral cavity cancer; metastatic squamous neck cancer with occult primary; multiple myeloma/plasma cell neoplasm' mycosis fungoides; myelodysplastic syndromes; myelodysplastic/myeloproliferative diseases; multiple myeloma; nasal cavity and paranasal sinus cancer; nasopharyngeal cancer; Non-Hodgkin's lymphoma; Non-Small Cell Lung cancer; oral cancer; oropharyngeal cancer; ovarian cancer; ovarian germ cell tumor; pancreatic cancer; primary central nervous system lymphoma; prostate cancer; small intestine cancer; squamous cell carcinoma; and Waldenstrom's Macroglobulinemia.

4. The method of claim **3**, wherein the cancer is selected from the group consisting of acute lymphoblastic leukemia; acute myeloid leukemia; breast cancer; chronic lymphocytic leukemia; colon cancer; colorectal cancer; cutaneous T-cell lymphoma; Ewing's sarcoma; gastric (stomach) cancer; head and neck cancer; hepatocellular (liver) cancer; Hodgkin's lymphoma; multiple myeloma; nasopharyngeal cancer; Non-Hodgkin's lymphoma; Non-Small Cell Lung cancer; oral cancer; ovarian cancer; pancreatic cancer; squamous cell carcinoma; and prostate cancer.

5. The method of claim **3**, wherein the cancer is selected from the group consisting of breast cancer; colon cancer; colorectal cancer; head and neck cancer; hepatocellular (liver) cancer; multiple myeloma; Non-Small Cell Lung cancer; ovarian cancer; squamous cell carcinoma; and prostate cancer.

6. The method of claim **1**, wherein the cancer is selected from the group consisting of adrenocortical carcinoma; anal cancer; basal cell carcinoma; bladder cancer; breast cancer; bronchial adenomas/carcinoids; cervical cancer; colon cancer; colorectal cancer; endometrial cancer; esophageal cancer; extrahepatic bile duct cancer; gallbladder cancer; gastric (stomach) cancer; gastrointestinal carcinoid tumor; gestational trophoblastic tumor; head and neck cancer, hepatocellular (liver) cancer; hypopharyngeal cancer; kidney (renal cell) cancer; laryngeal cancer; lip and oral cavity cancer; metastatic squamous neck cancer with occult primary; multiple endocrine neoplasia syndrome; nasal cavity and paranasal sinus cancer; nasopharyngeal cancer; Non-Small Cell Lung cancer; oral cancer; oropharyngeal cancer; pancreatic cancer; parathyroid cancer; penile cancer; pituitary tumor; prostate cancer; rectal cancer; salivary gland cancer; skin carcinoma, Merkel Cell; small cell lung cancer; small intestine cancer; squamous cell carcinoma; thymoma; thymoma and thymic carcinoma; thyroid cancer; transitional cell cancer of the renal pelvis and ureter; urethral cancer; uterine cancer, endometrial; vaginal cancer; vulvar cancer; and Wilms' Tumor.

7. The method of claim **6**, wherein the cancer is selected from the group consisting of breast cancer; colon cancer; colorectal cancer; gastric (stomach) cancer; head and neck cancer, hepatocellular (liver) cancer; metastatic squamous neck cancer with occult primary; nasopharyngeal cancer; Non-Small Cell lung cancer; oral cancer; pancreatic cancer; prostate cancer; and squamous cell carcinoma.

8. The method of claim **1**, wherein the cancer is selected from the group consisting of acute lymphoblastic leukemia; acute myeloid leukemia; AIDS-related lymphoma; Burkitt's lymphoma; chronic lymphocytic leukemia; chronic myelogenous leukemia; chronic myeloproliferative disorders; cutaneous T-cell lymphoma; hairy cell leukemia; hematologic

(blood) cancer; Hodgkin's lymphoma; multiple myeloma/plasma cell neoplasm' mycosis fungoides; myelodysplastic syndromes; myelodysplastic/myeloproliferative diseases; multiple myeloma; Non-Hodgkin's lymphoma; primary central nervous system lymphoma; Sezary Syndrome; and Waldenstrom's Macroglobulinemia.

9. The method of claim **8**, wherein the cancer is selected from the group consisting of acute lymphoblastic leukemia; acute myeloid leukemia; chronic lymphocytic leukemia; cutaneous T-cell lymphoma; hematologic (blood) cancer; Hodgkin's lymphoma; multiple myeloma; and Non-Hodgkin's lymphoma.

10. The method of claim **8**, wherein the cancer is multiple myeloma.

11. The method of claim **1**, wherein the cancer is selected from the group consisting of Ewing's sarcoma; Kaposi's Sarcoma; osteosarcoma/malignant fibrous histiocytoma of bone; soft tissue sarcoma; and uterine sarcoma.

12. The method of claim **11**, wherein the cancer is Ewing's sarcoma.

13. The method of claim **1**, wherein the cancer is selected from the group consisting of extracranial germ cell tumor; extragonadal germ cell tumor; ovarian cancer; ovarian epithelial cancer; ovarian germ cell tumor; and testicular cancer.

14. The method of claim **13**, wherein the cancer is ovarian cancer.

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